Strategies for the Treatment of Lyme Disease

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2nd International Lyme & Associated Diseases Society (ILADS) Educational Meeting Europe
May 28, 2011
8:40am – 9:25am
Augsburg, Germany
at the Augustana Saal, Annahof Augsburg

Steven Harris, MD

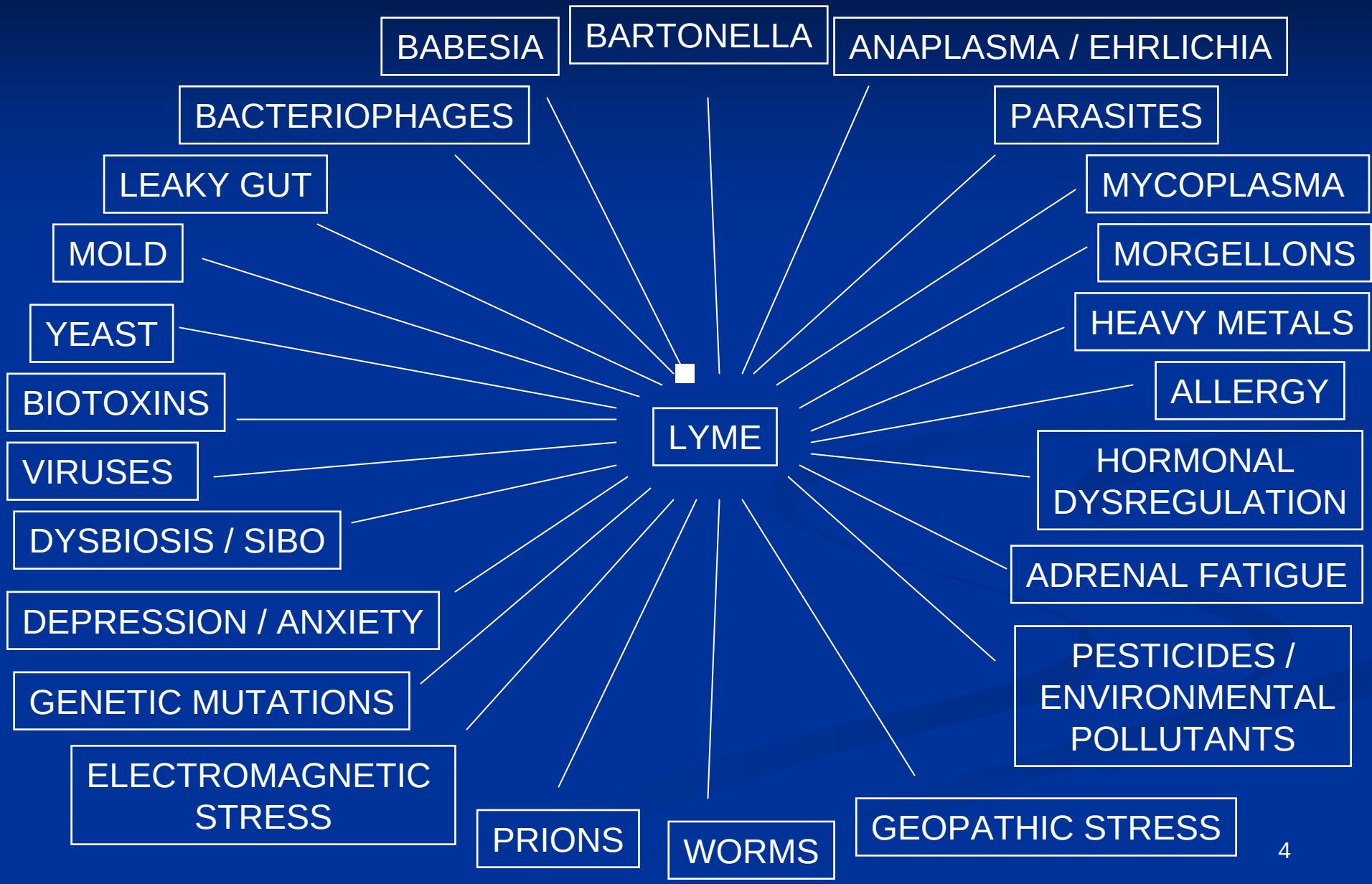
Affiliations

- IGeneX, Inc. - clinical consultant
- QMedRx - medical advisory board
- Pacific Frontier Medical, Inc - CEO

Lyme Disease

- The discipline of Lyme disease including investigations into the extent of this disease and its optimal treatment is still in its infancy. There have been scarcely two fractional generations of clinicians who are confronting the full nature of this affliction.

Interactions



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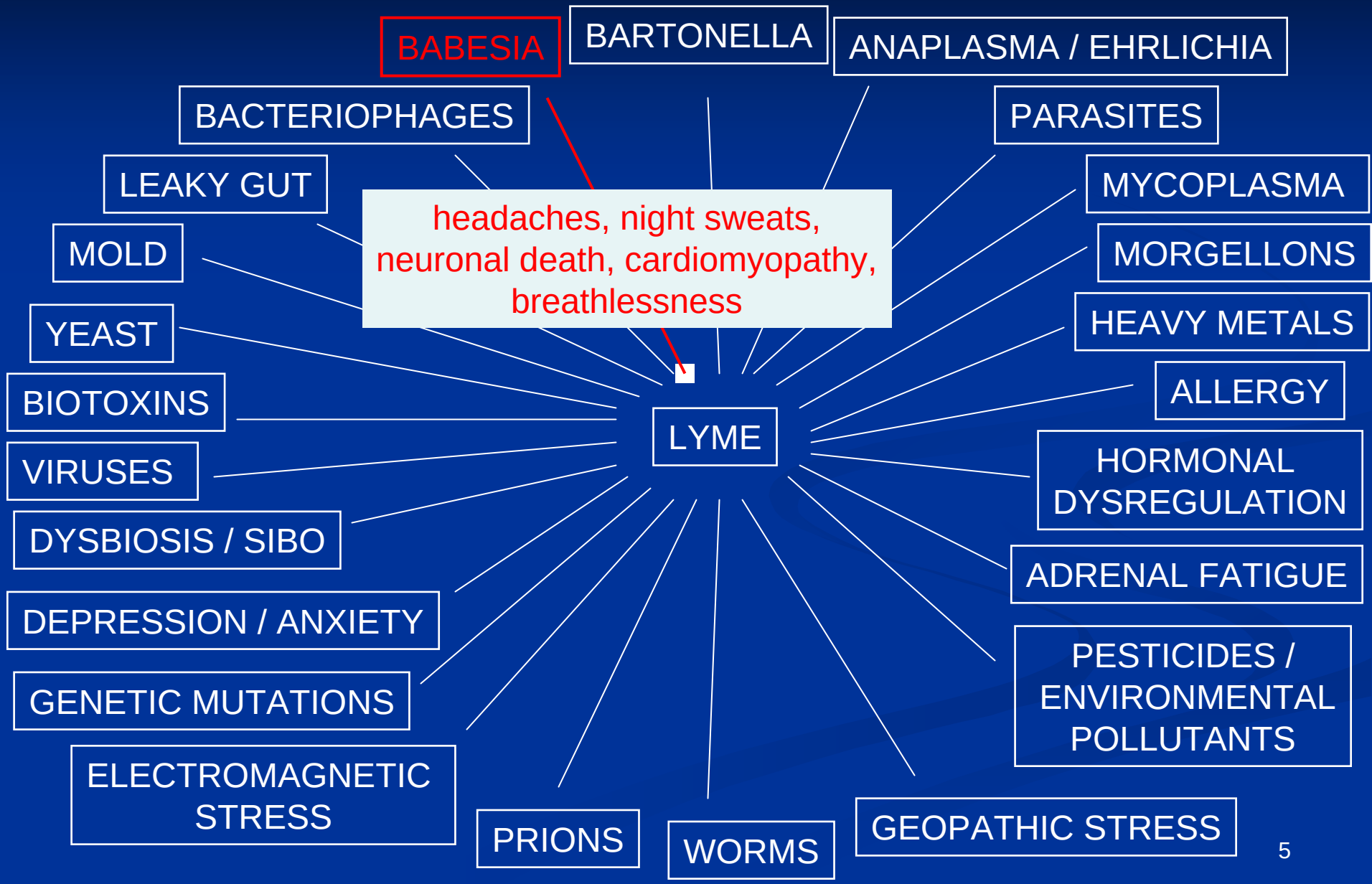

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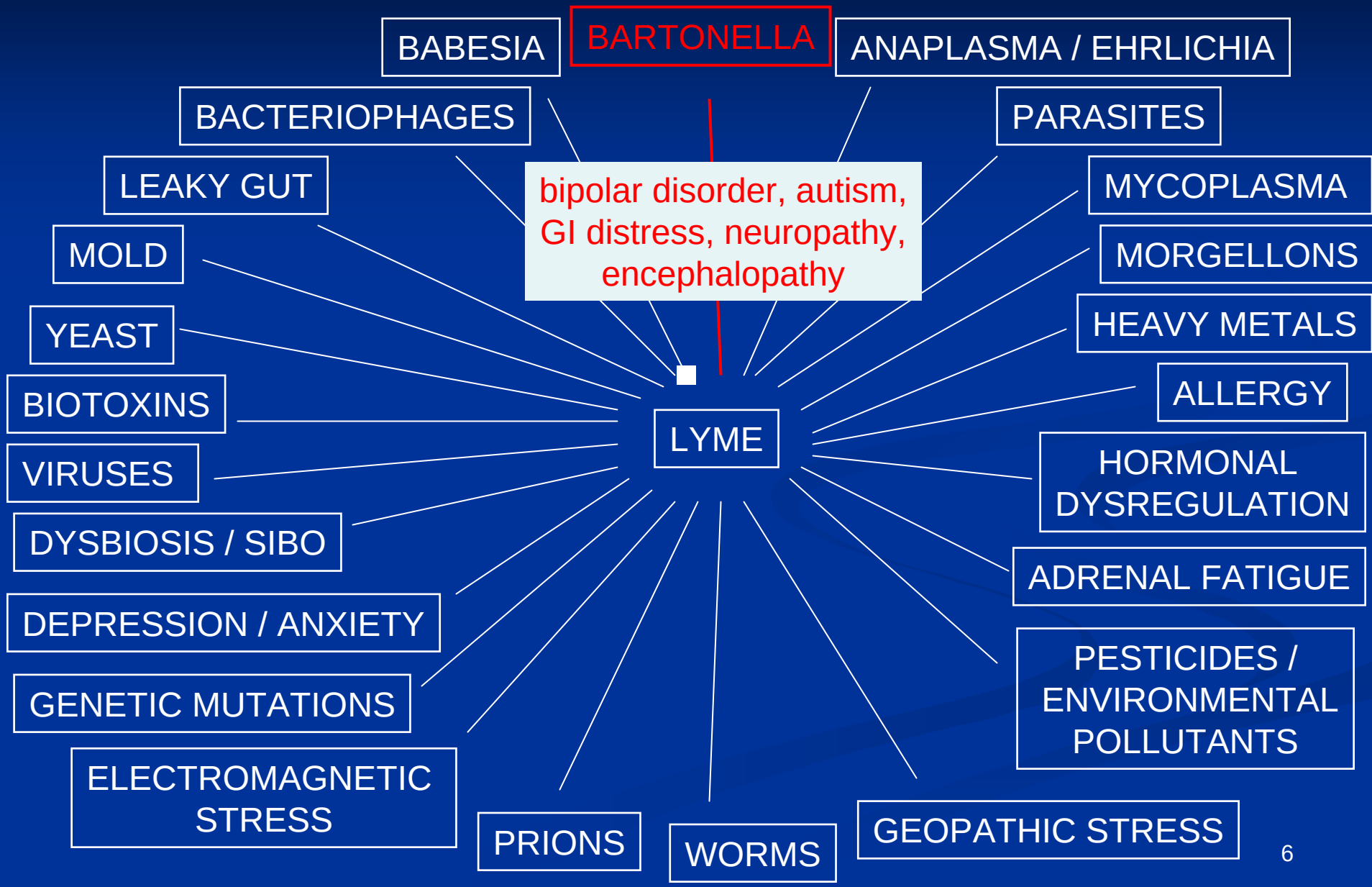

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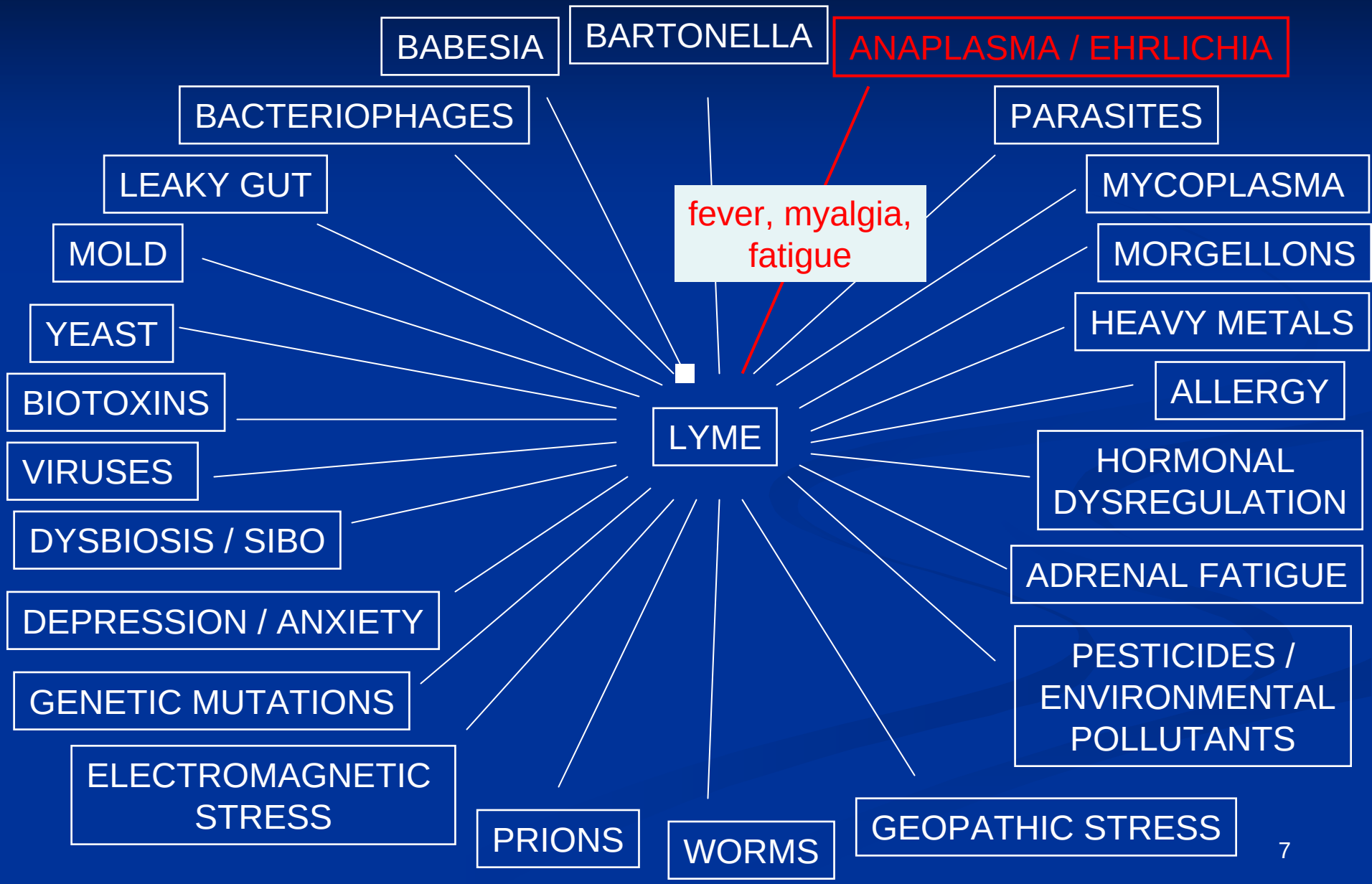

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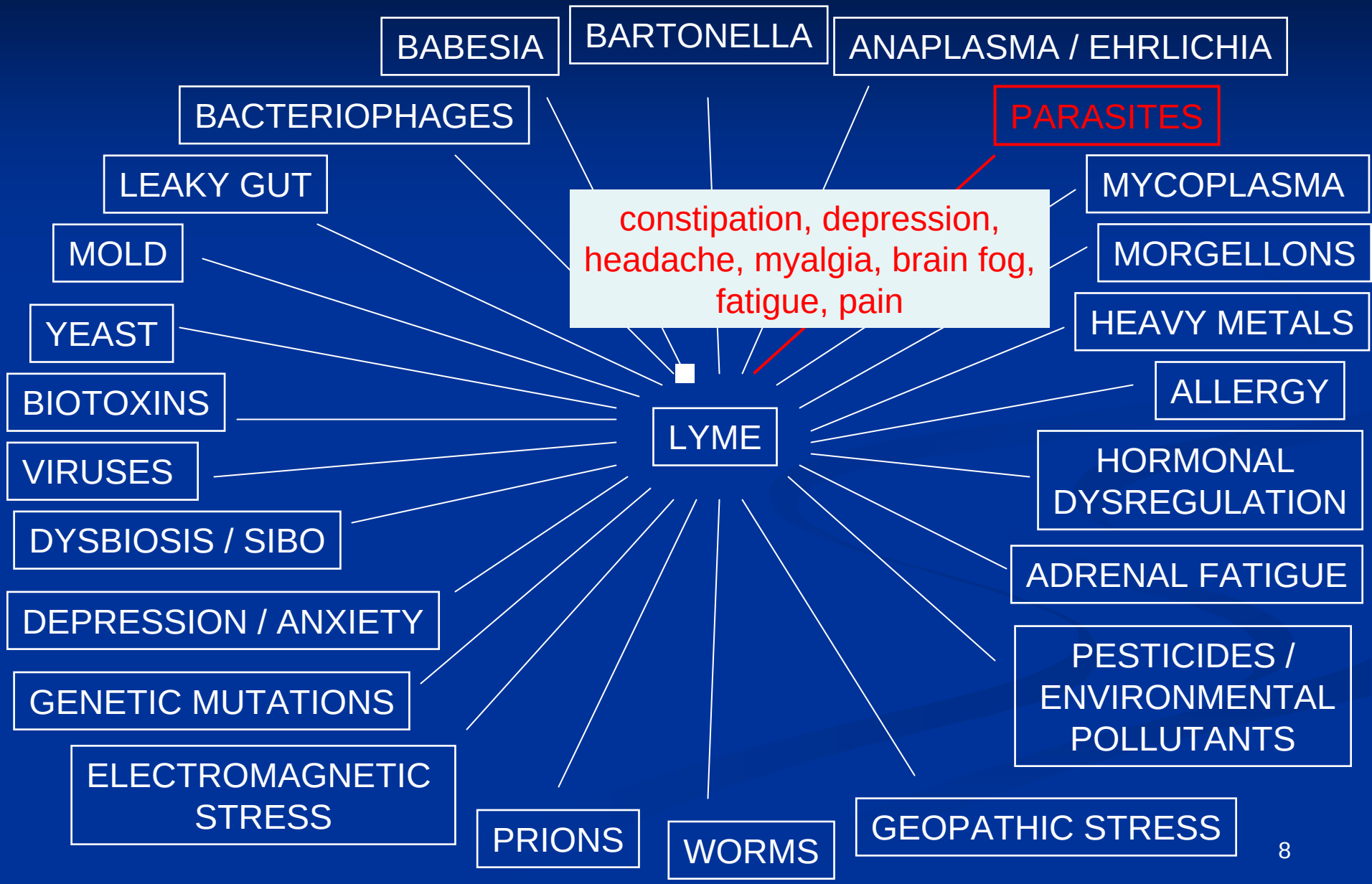

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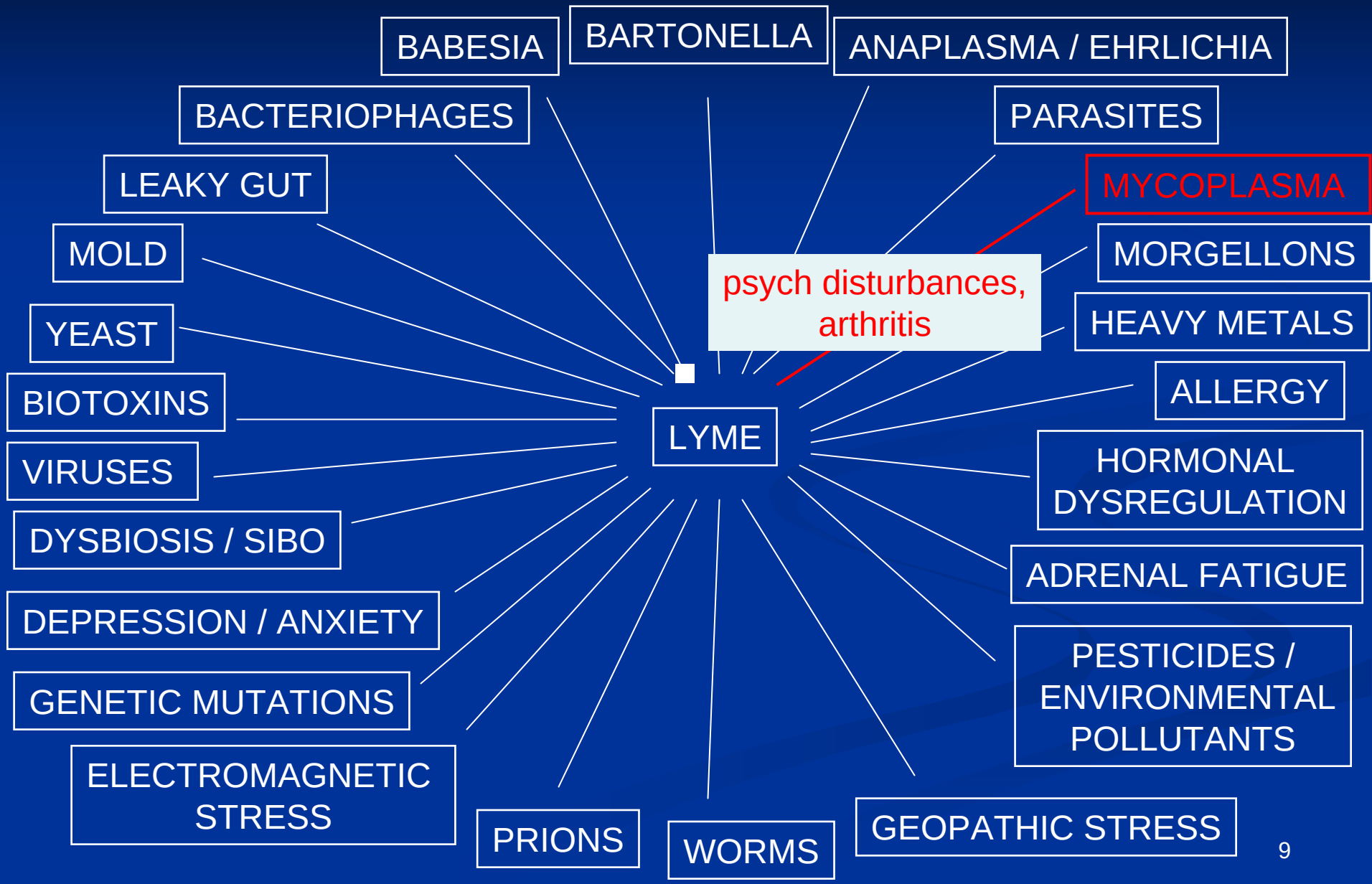

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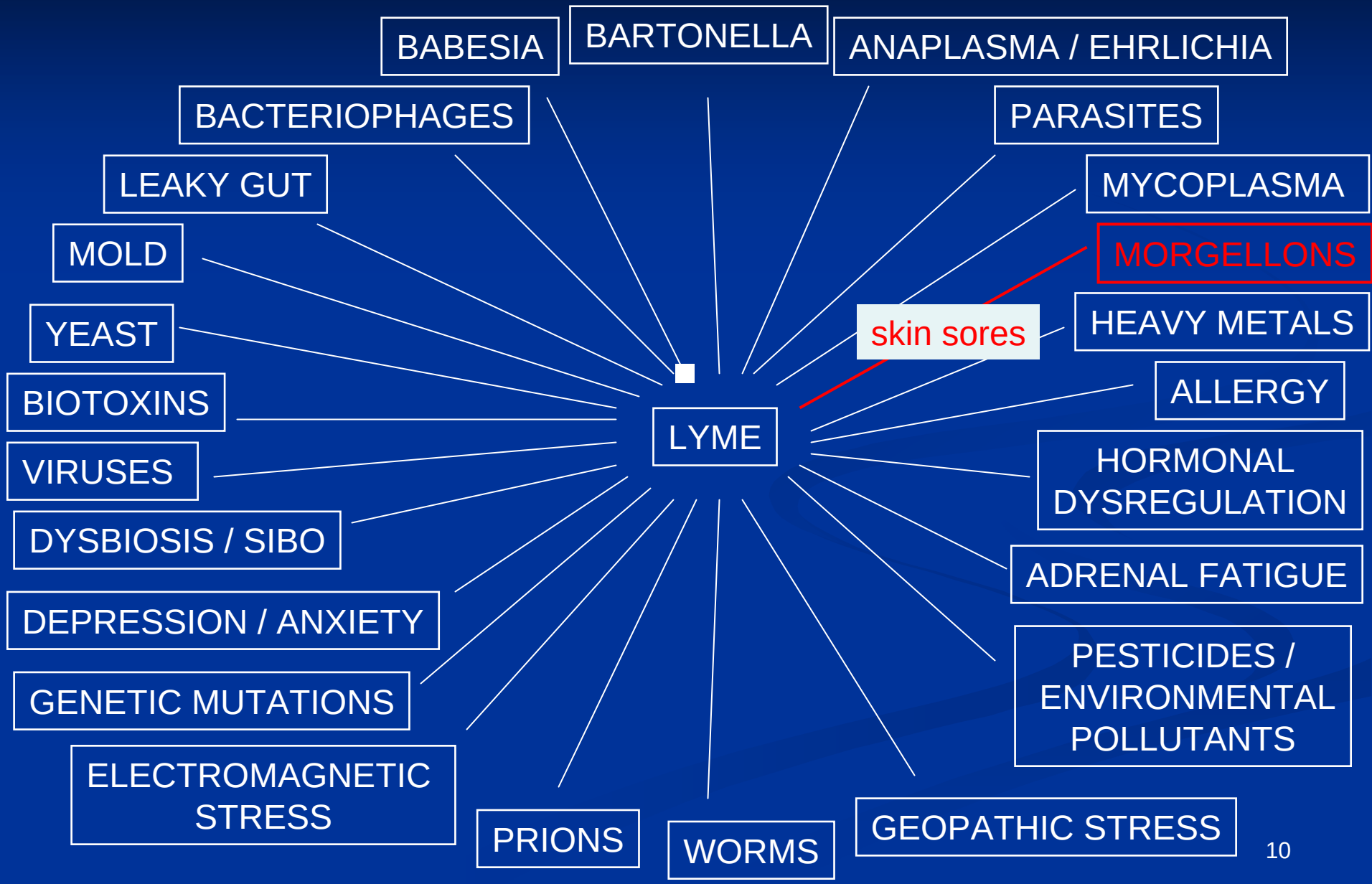

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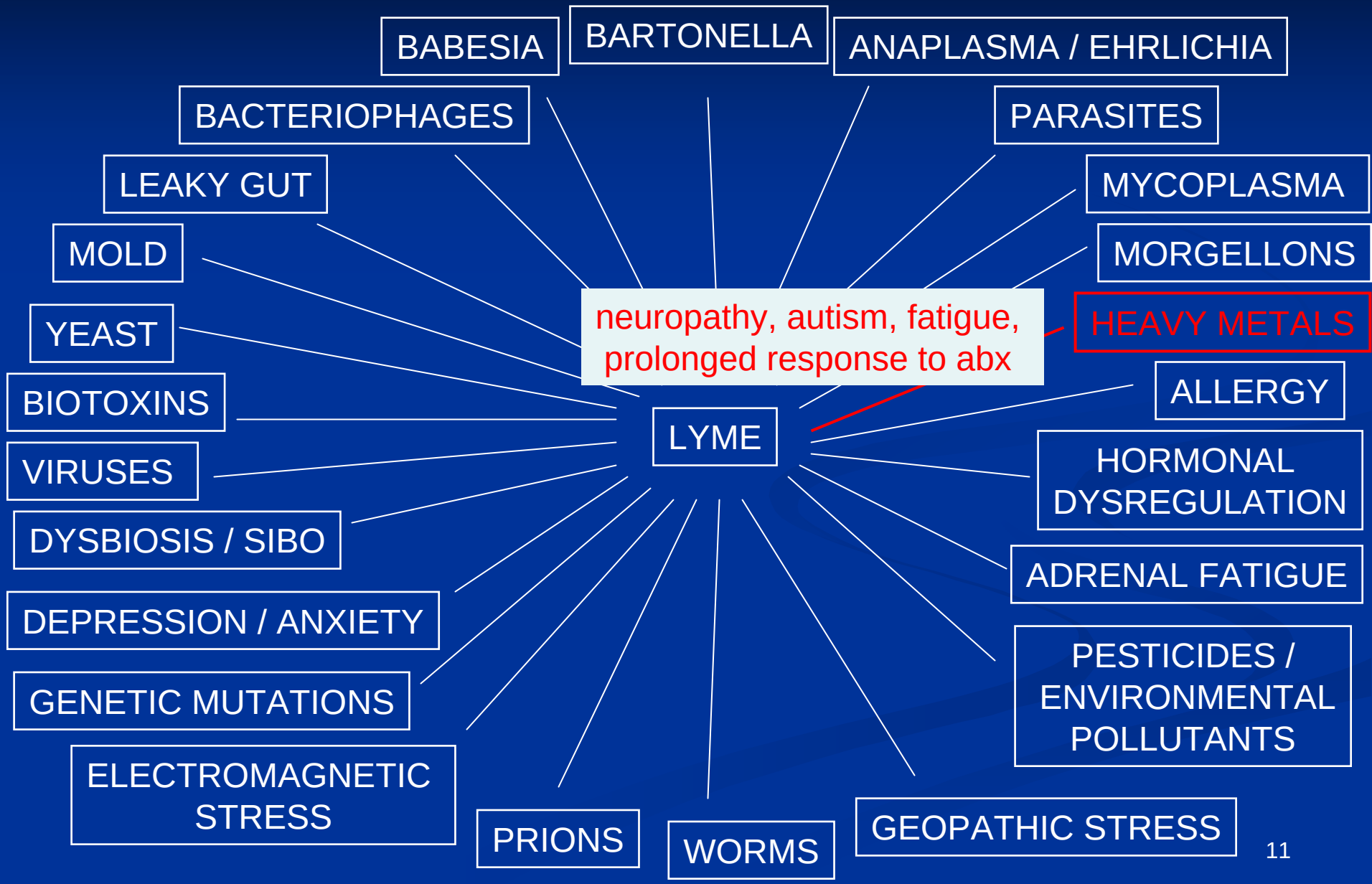

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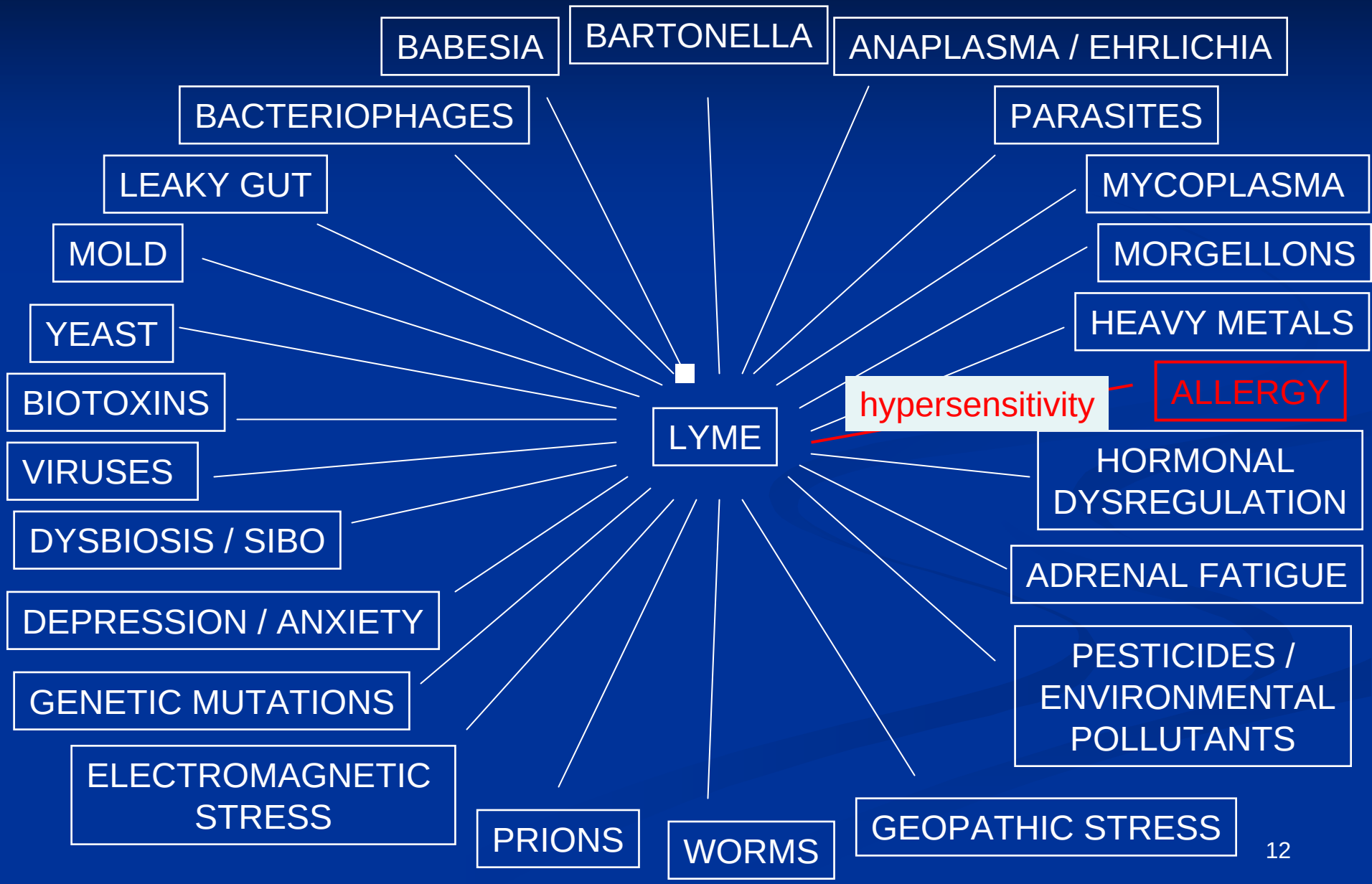

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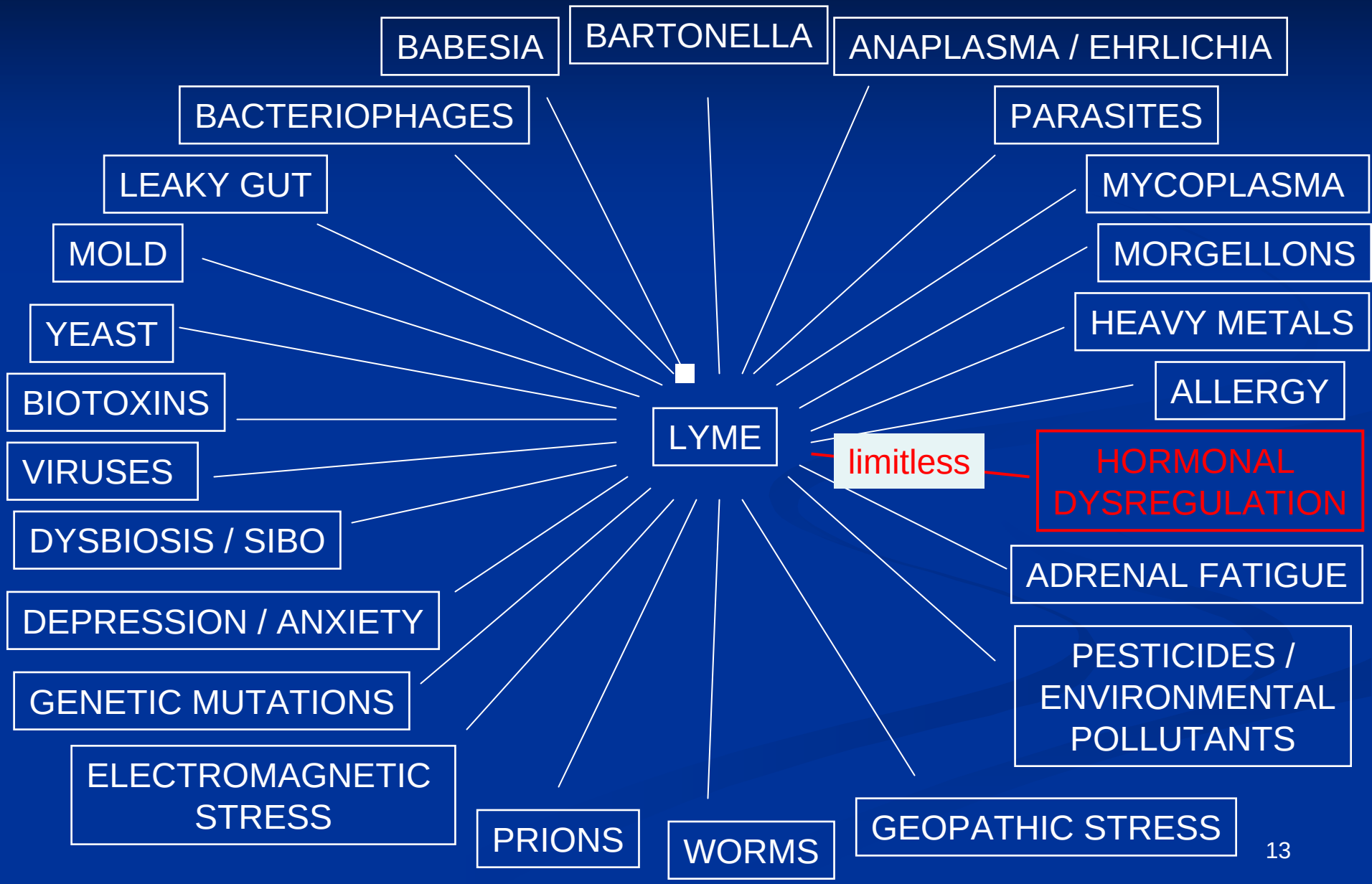

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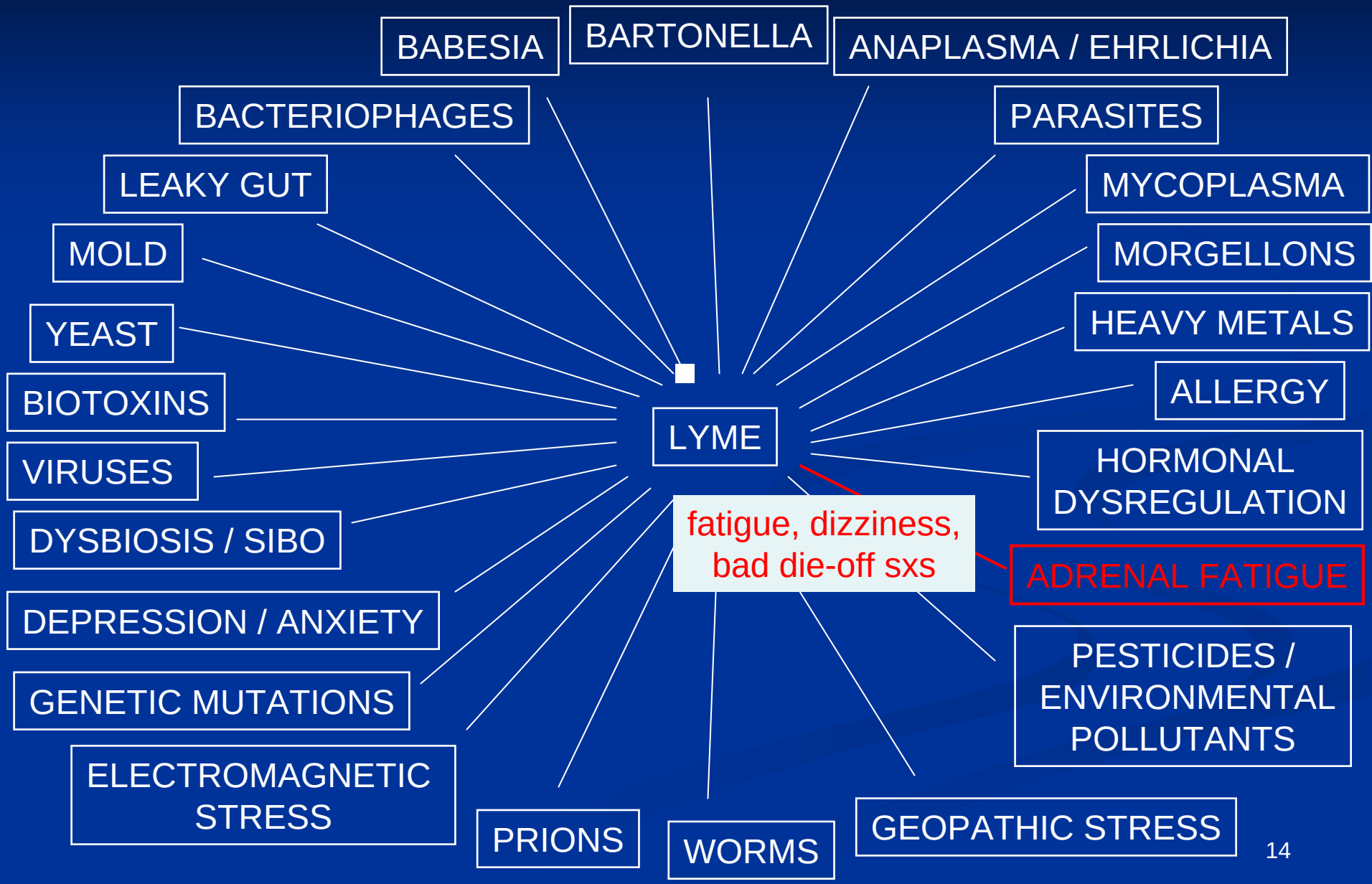

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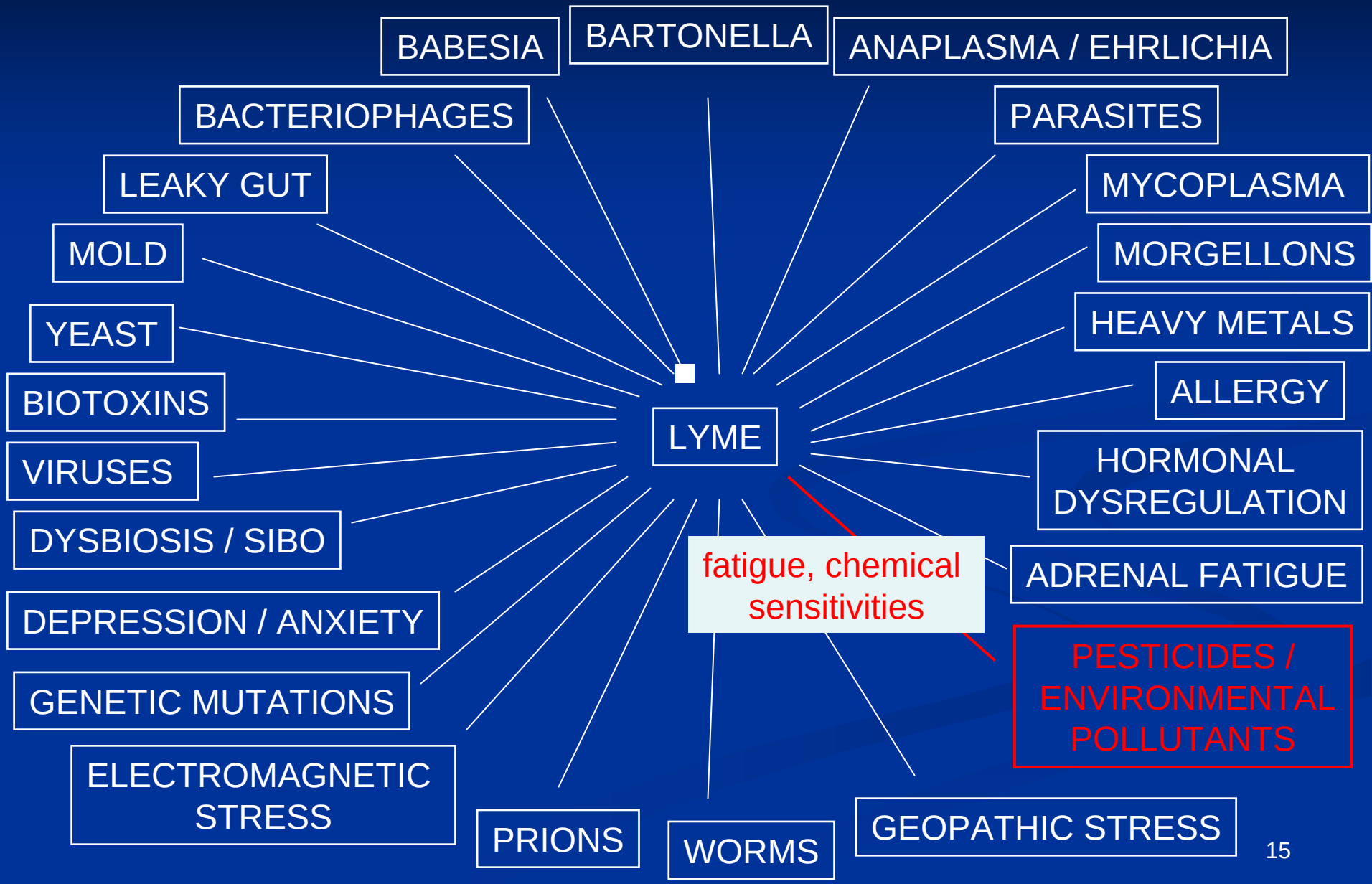

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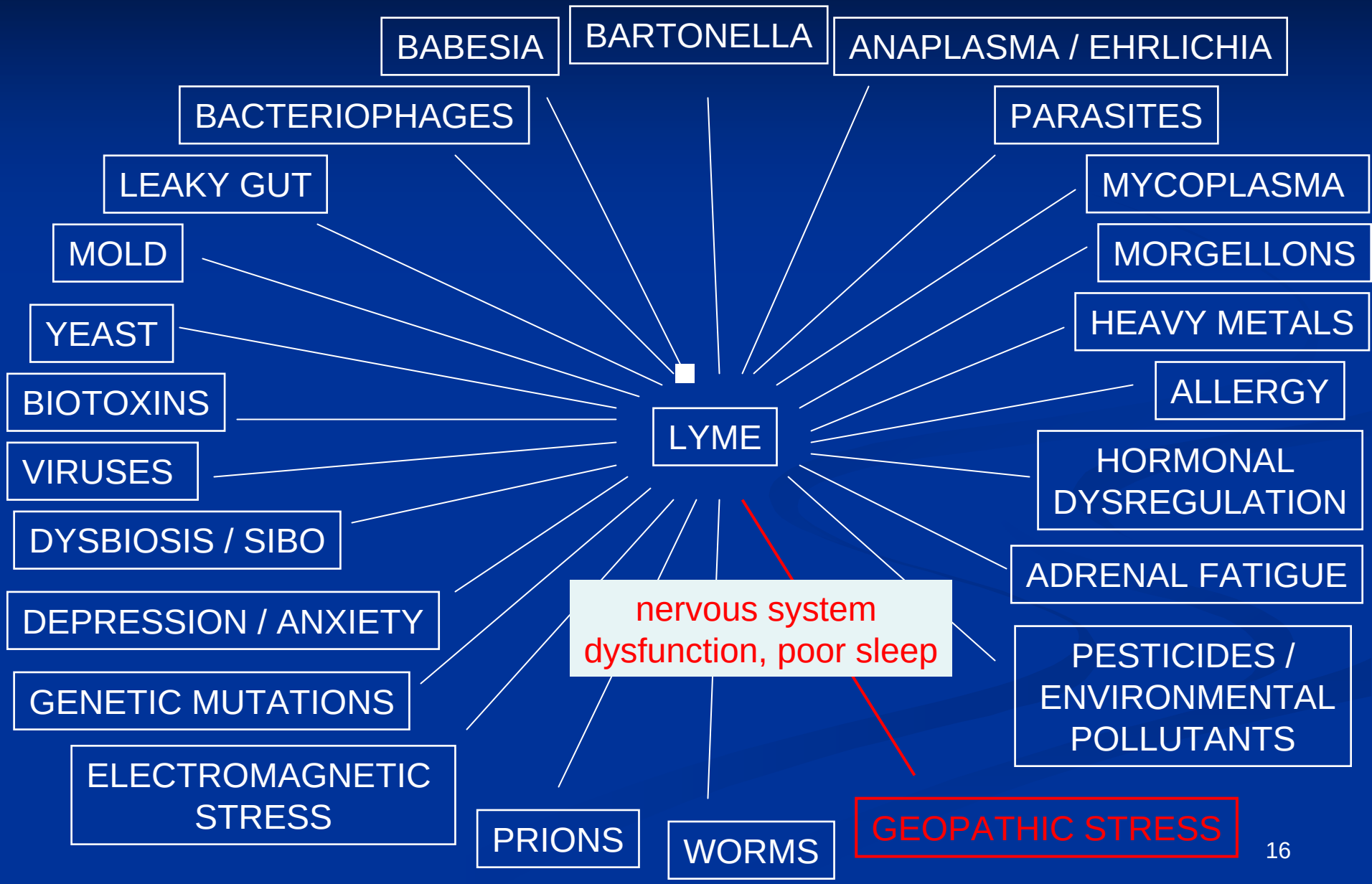

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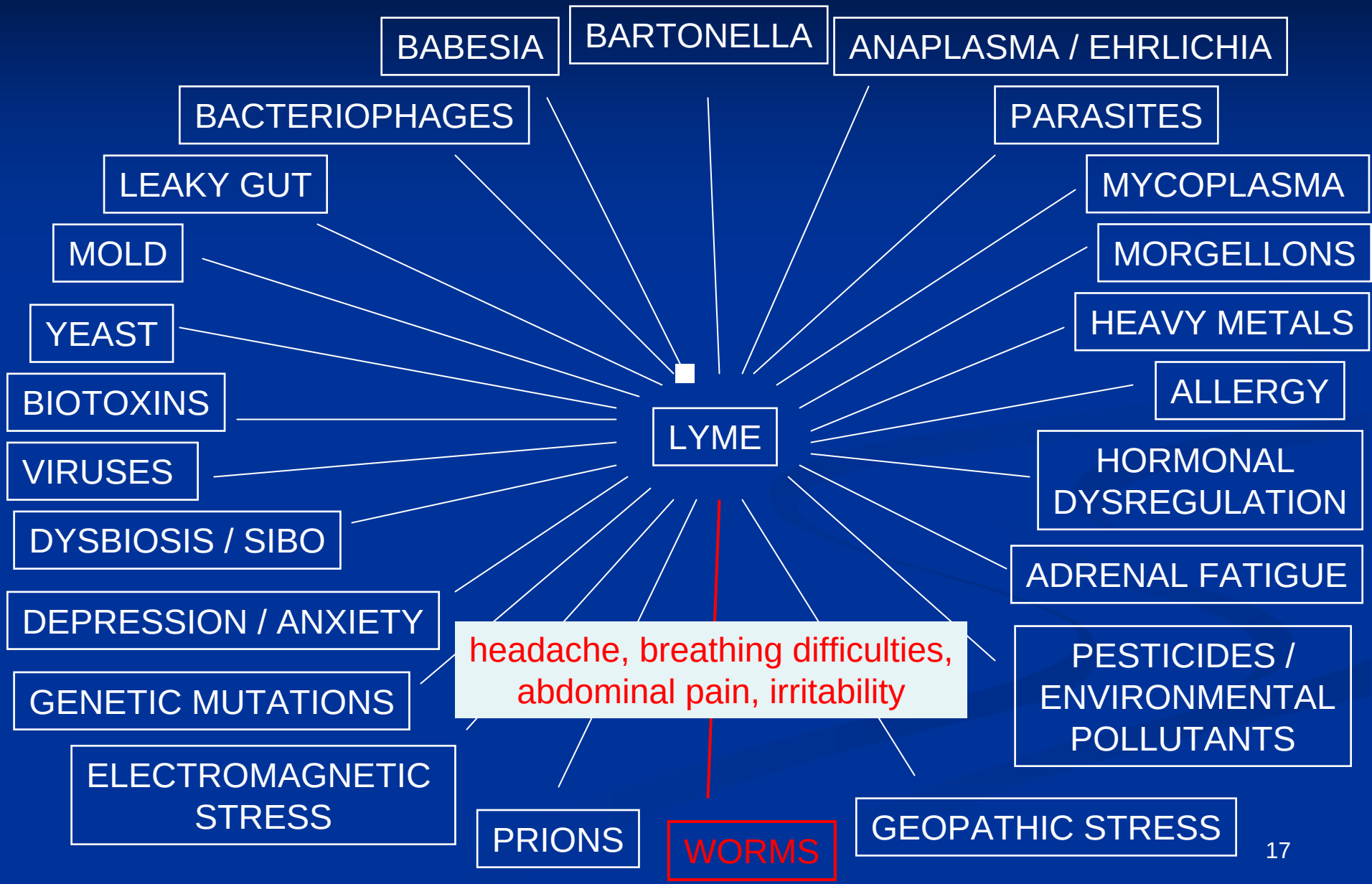

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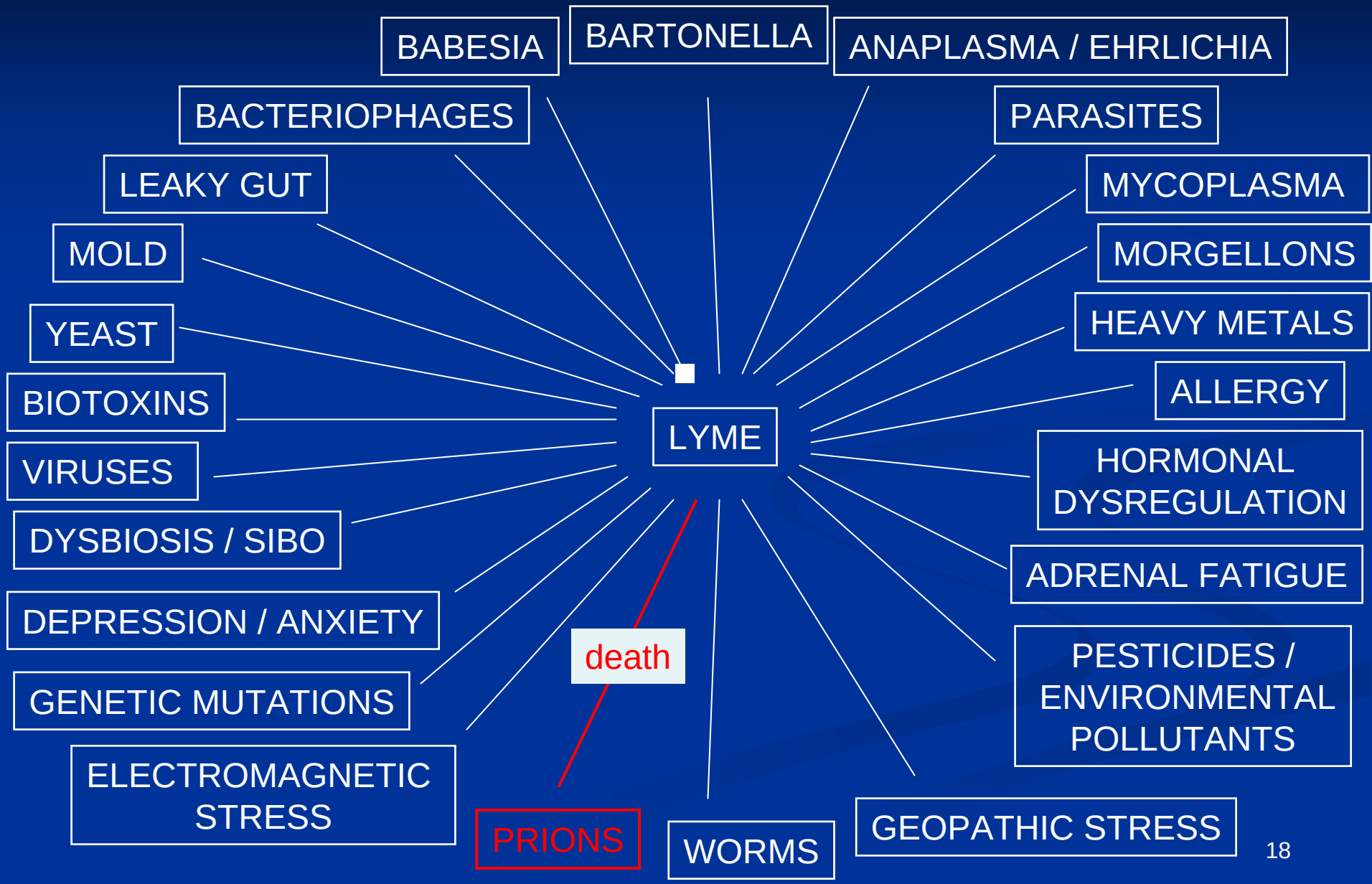

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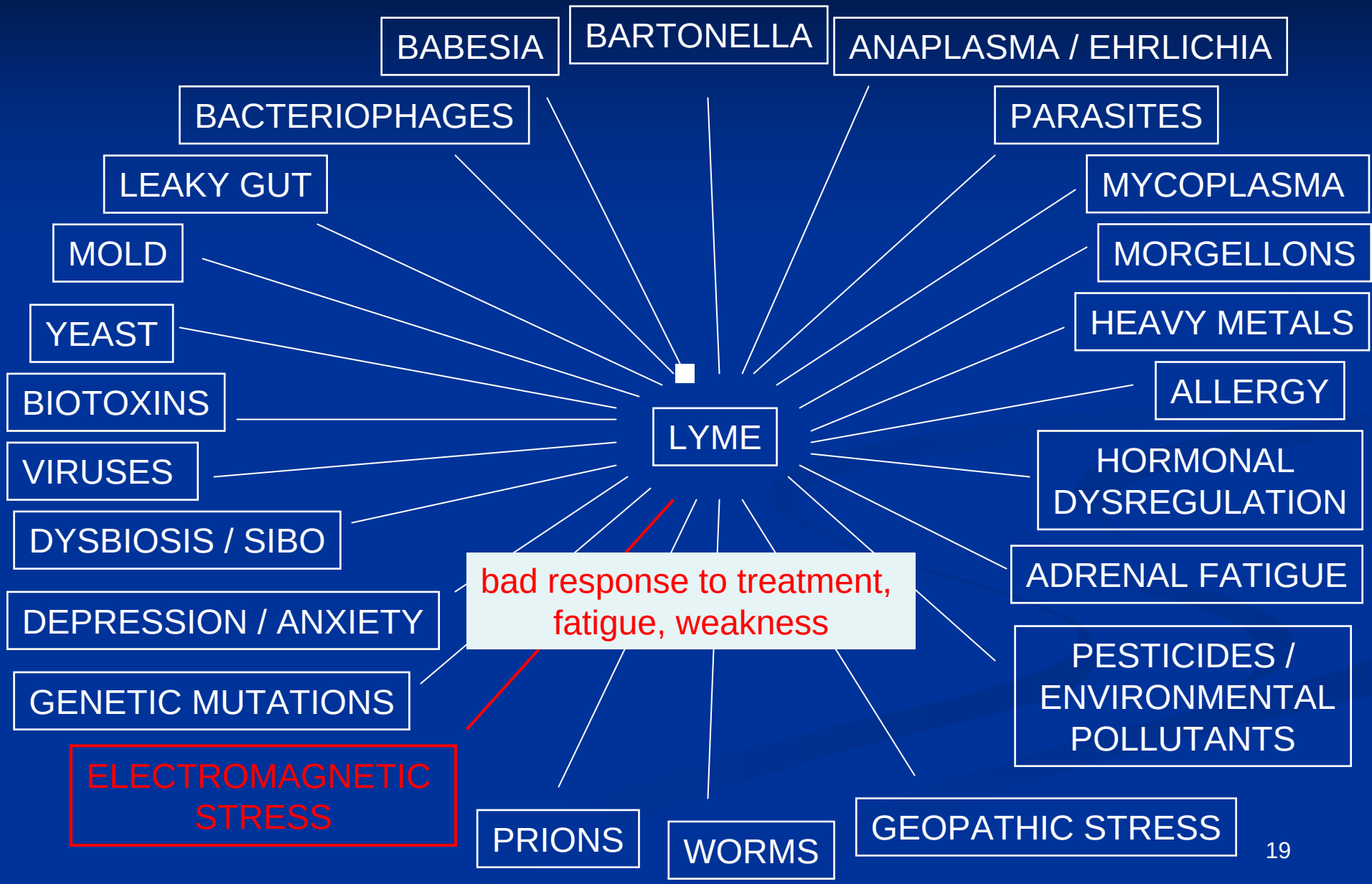

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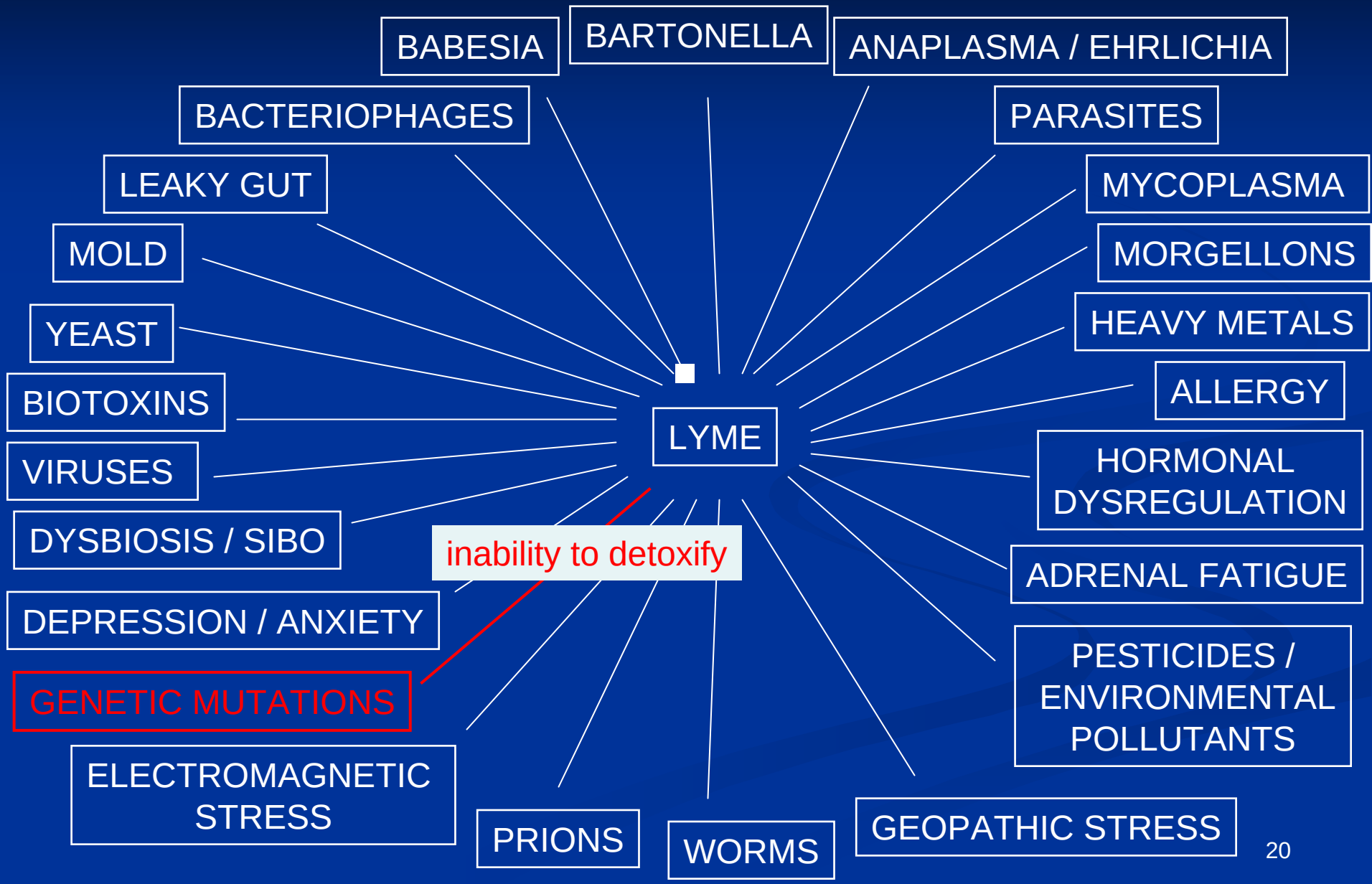

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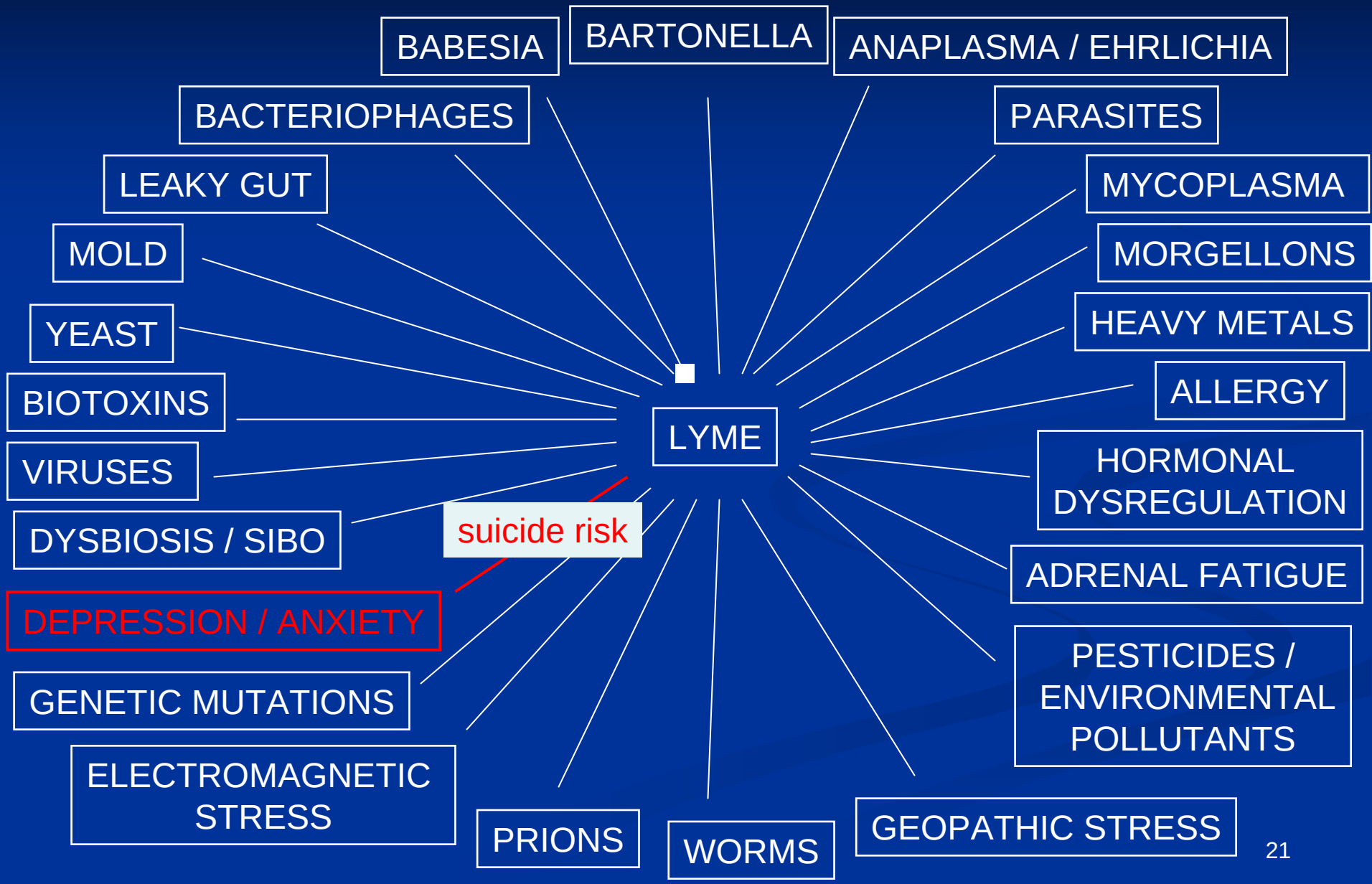

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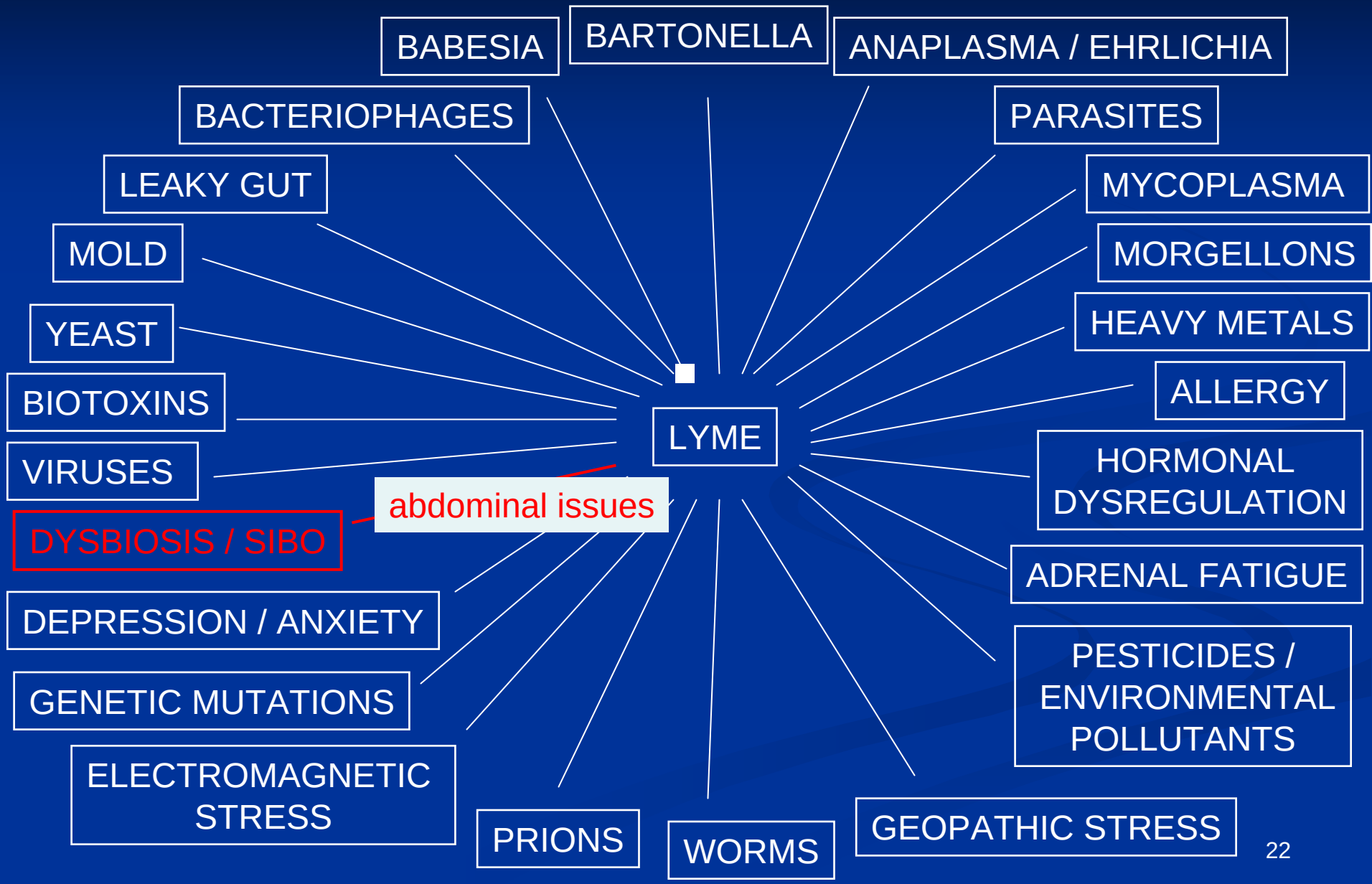

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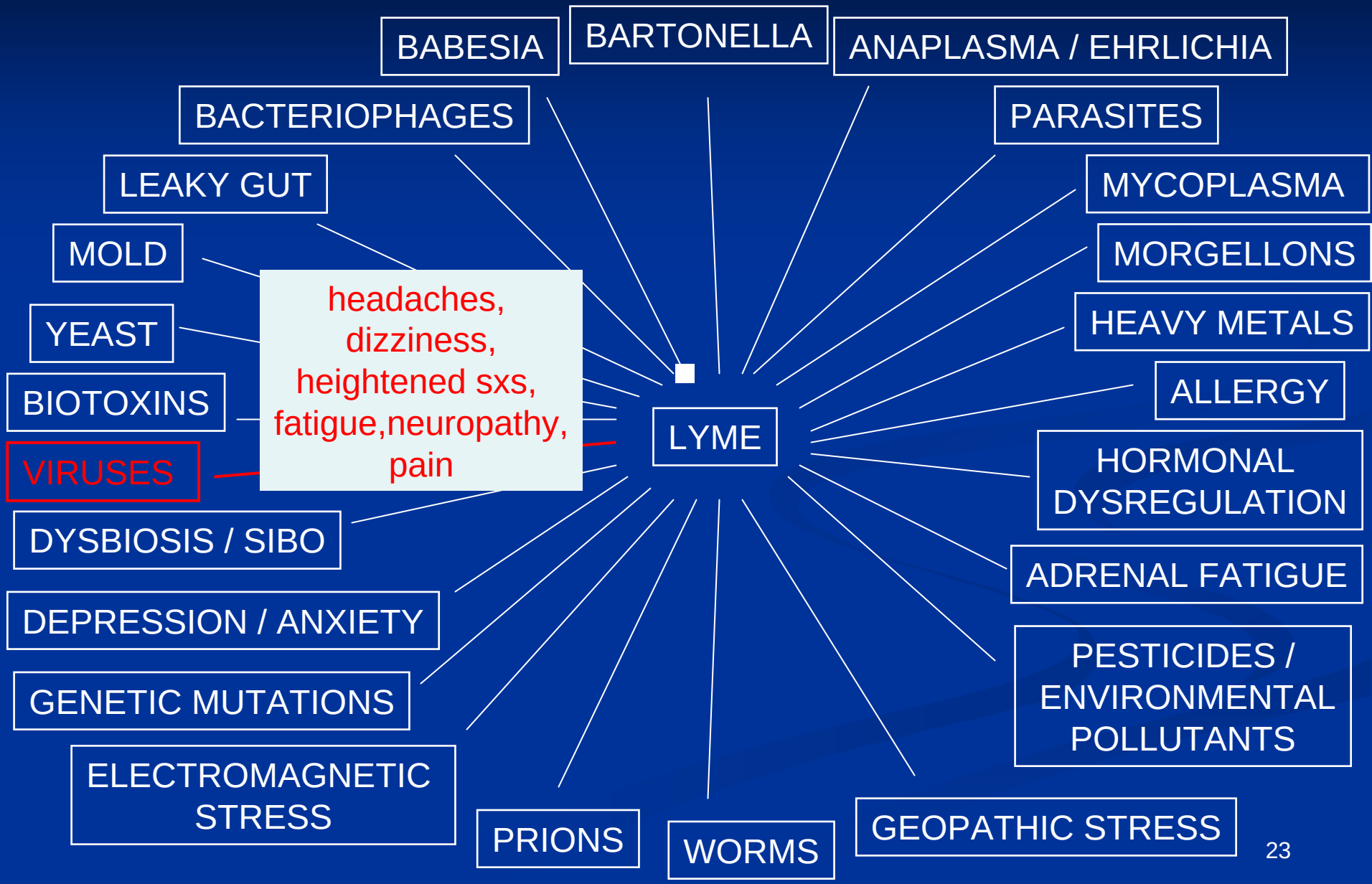

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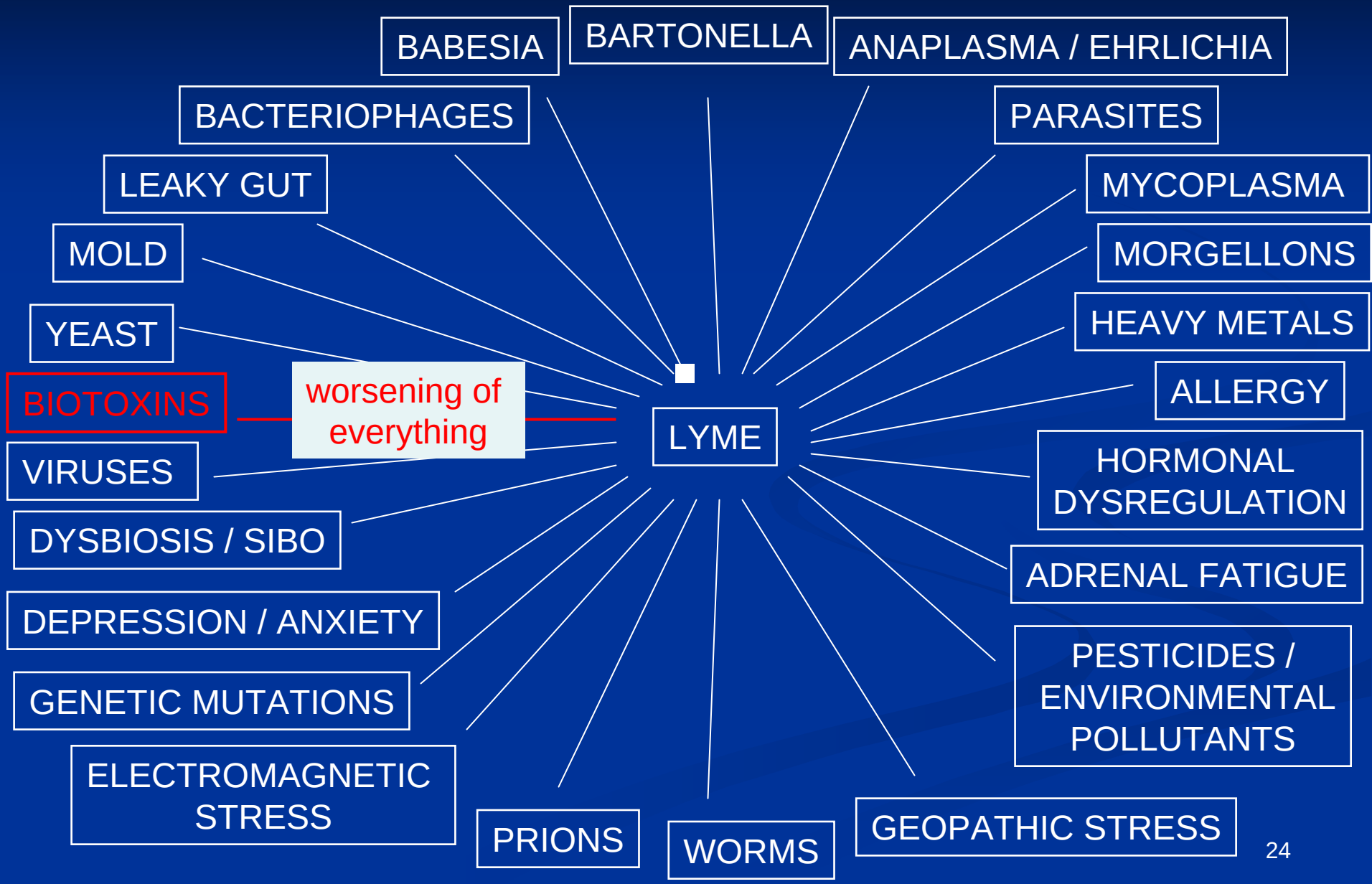

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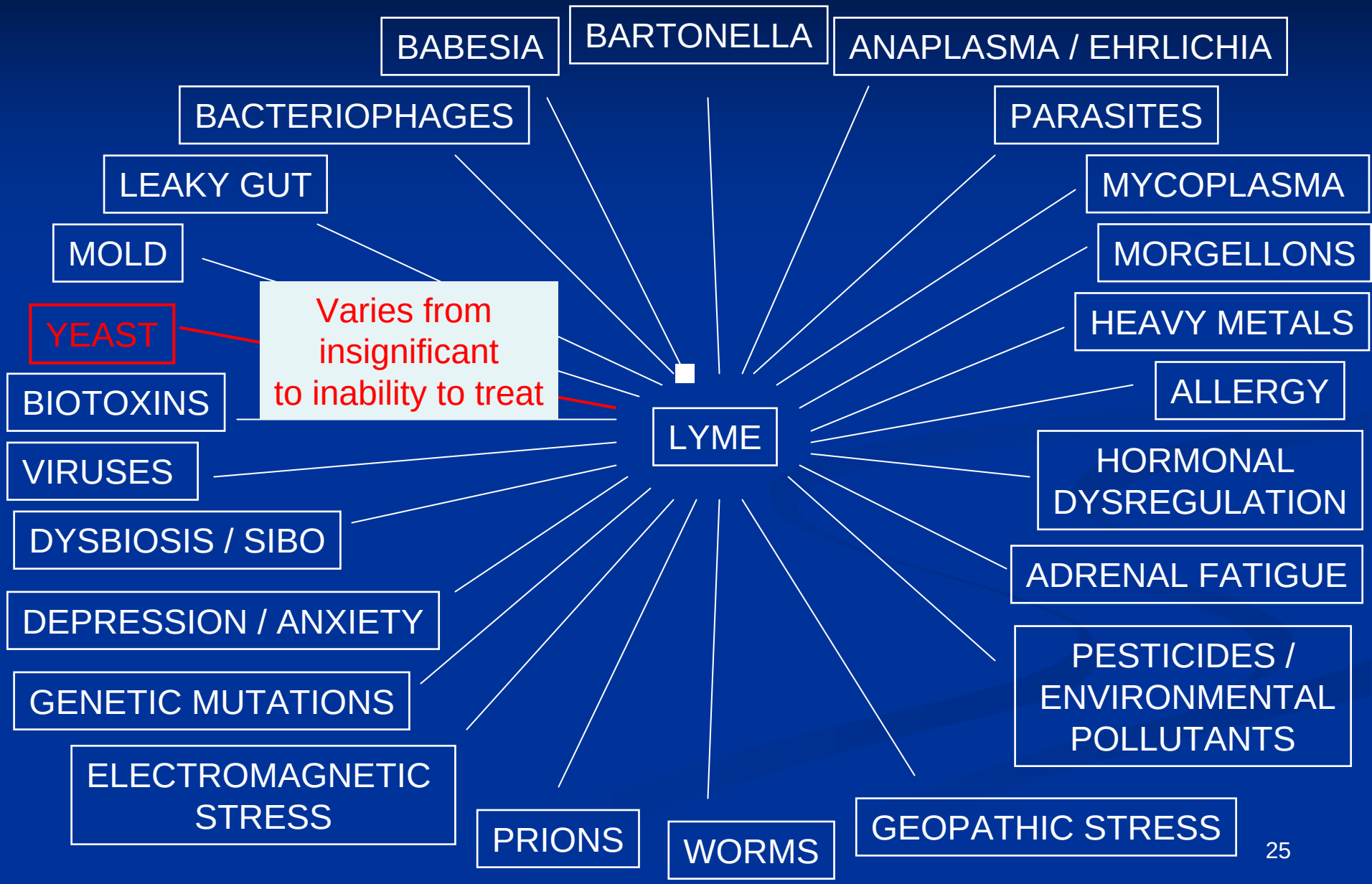

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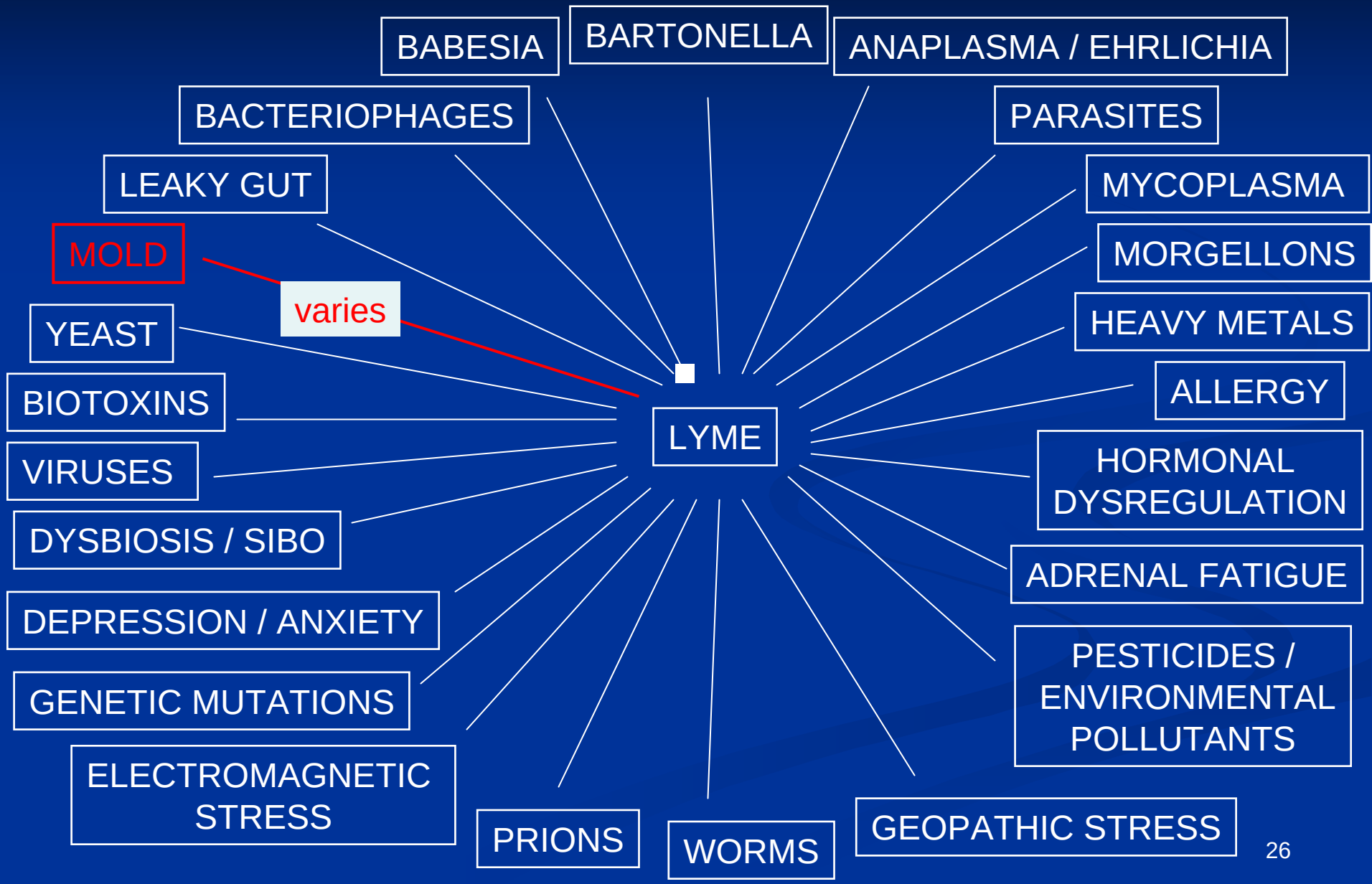

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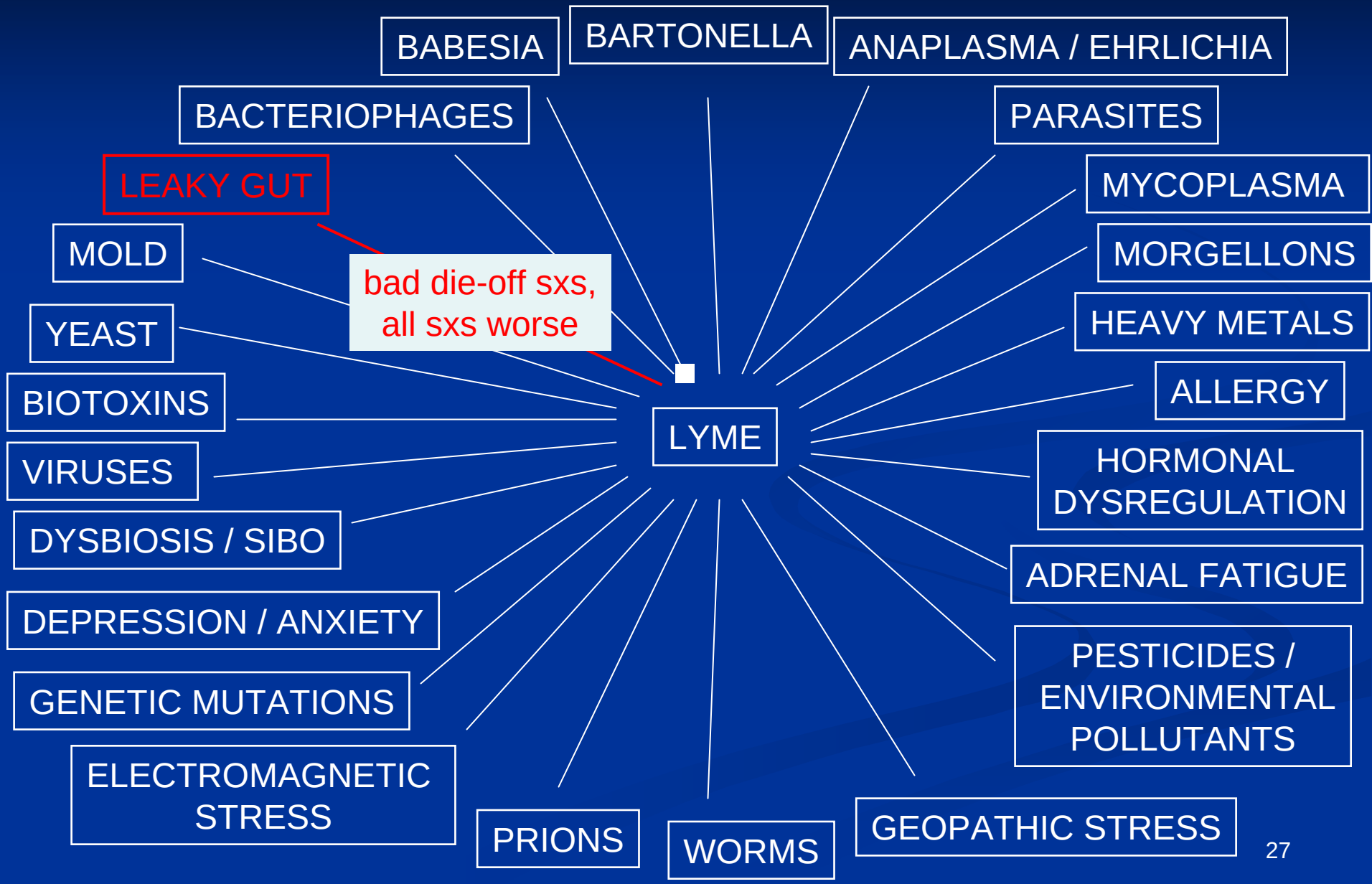

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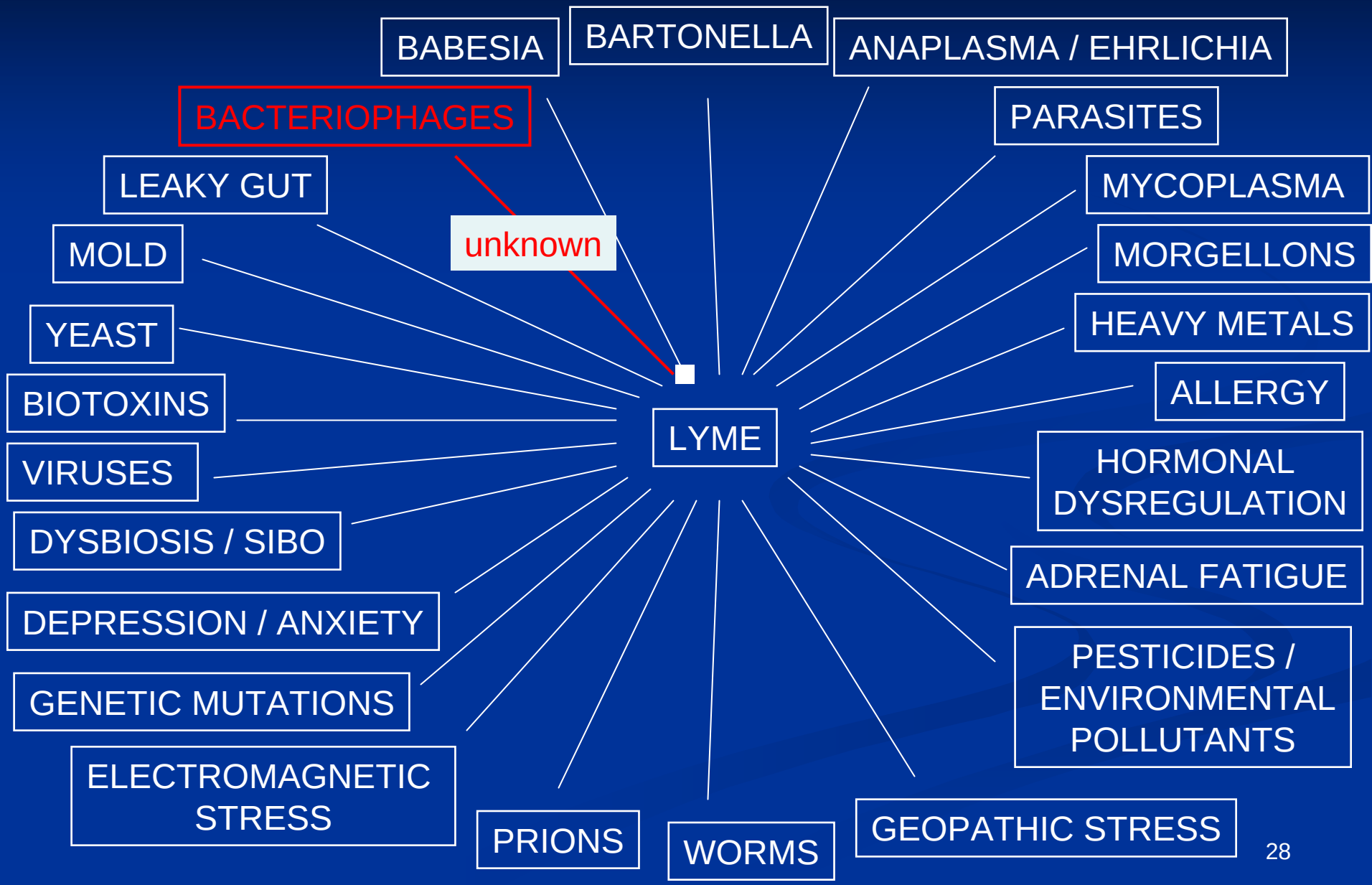


What can the clinical state of the infection mimic?

- Lupus
- Rheumatoid arthritis
- Polymyalgia rheumatica
- Polymyositis/dermatomyositis
- CFIDS
- Fibromyalgia
- Multiple Chemical Sensitivity
- Bipolar d/o
- ADHD
- Autism
- Chronic EBV
- Schizoaffective d/o

- Multiple sclerosis
- CIDP
- Amyotrophic lateral sclerosis
- Alzheimer's disease
- Parkinson's Disease
- Thyroid disease
- Addison's disease
- Hyperparathyroidism
- Reflex sympathetic dystrophy
- Menopause

If Lyme can mimic so many diseases, how can it be diagnosed?

A Lyme patient will usually experience 6-40+ symptoms at a time.

Some wax and wane.

- Joint pain
- Joint stiffness
- Joint swelling
- Lightheadedness
- Fevers / Chills
- GI upset
- Pelvic pain
- Blurry vision
- Myoclonus
- Fasciculations
- Severe depression (depressive episode)
- Body electric
- Word-finding problems
- Dysuria

If Lyme can mimic so many diseases, how can it be diagnosed?

Some symptoms tend to remain constant.

- Fatigue
- Sleep disturbance
- Headache
- Tinnitus
- Muscle pain
- Worsening symptoms 4 days before menses
- Neck pain (buffalo hump pain)
- Joint crepitus
- Low frustration tolerance
- Poor executive functioning
- Low libido
- Hypoesthesia (regions of numbness)
- Hyperacusis

If Lyme can mimic so many diseases, how can it be diagnosed?

Some symptoms are variable.

Many patients will constantly experience these symptoms.
Other patients will sporadically experience them.

- Dysthymia
- Neuropathic pain
- Restless leg
- Tremor
- Anxiety
- Encephalopathy

- Subdermal fibrous cysts
- Osteophytes
- Blood pressure instability
- Autonomic dysreflexia
- Muscle weakness
- Abdominal pain

If Lyme can mimic so many diseases, how can it be diagnosed?

1. **Establish likely exposure**
   - Leisure activities
   - Residence vacations
   - Pets (are they sick?)
   - Occupation

2. **Ascertain prior experience with antibiotics**
   - Improvement
   - Worsening symptoms
   - No change

3. **Focus on life events surrounding transition from wellness to illness**
   - Surgeries
   - Accidents
   - Hiking trips
   - Steroids
   - Root canals

What To Look For During An Exam
Lyme

- Diffuse myofascial tenderness
- Increased fluid pressure on ballottement of fundi
- Adies pupil
- Oscillating pupils
- Hyperreflexia
- Vertical ridging in nails
- Clammy hands and feet
- Hypothermia 96.0-97.9
- Joint fluctuance – fingers, elbows, knees
- Joint crepitus
- Arrhythmia
- Nerve palsy CN 3,4,6,7,8
- Paraspinal spasms – especially C7

What To Look For During An Exam
Lyme

- Skin mottling
- Hypermelanosis
- Psoriasis
- Dermographia
- Horizontal nystagmus
- Thrush (co-habitation by yeast is common)
- Oiling of skin
- Abdominal distension
- Non-pitting edema
- Brown exudate on teeth
- Plantar tenderness
- SI joint
- Myofascial bundles
- Hoffman reflex
- Cold acral extremities
- Black flecks within skin ulcers (Morgellons)
- Subdermal fibromas
- Vagus nerve instability: vasovagal, hypomotility

Laboratory support in diagnosis

- Lyme borreliosis appears identical to some conditions. The typical symptom patterns do not fit except for some pronounced symptoms.

- *Some examples include*:
  - Multiple sclerosis
  - ALS
  - Parkinson's disease
  - Rheumatoid arthritis
  - Dementia
  - Chronic fatigue without pain
  - Bipolar disorder
  - Recurrent acute aseptic meningitis
  - Charcot Marie-Tooth
  - Guillian Barre
  - Scleroderma

Laboratory support in diagnosis

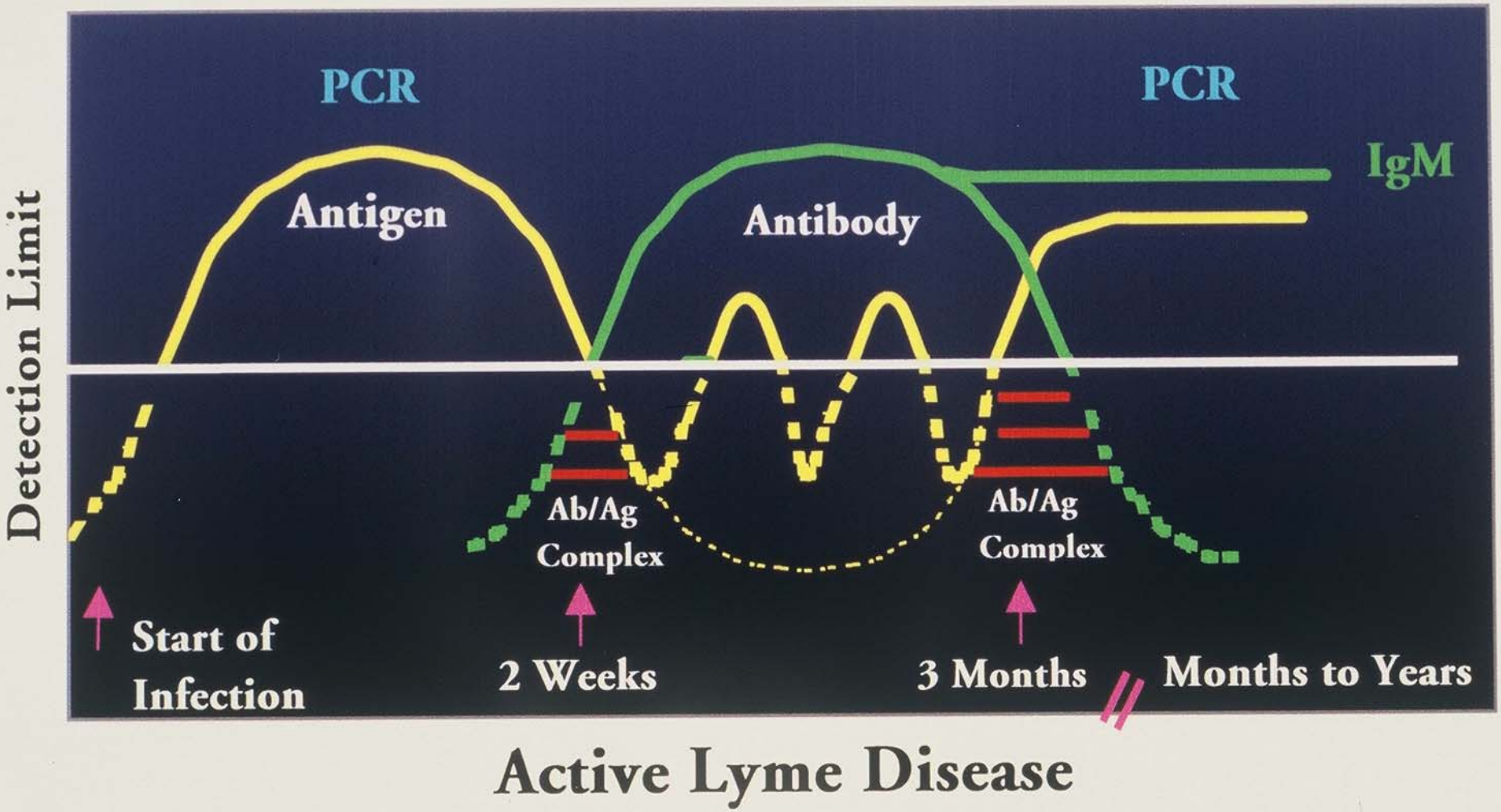
- In these situations lab support is crucial. One may find higher than 30% of these patients test positive for Lyme by antibodies, usually IgM Western blot, bands 31 kDa, 34 kDa, 23-25 kDa, 39 kDa, 58 kDa, 83-93 kDa in some combination **AND** Bb PCR in either serum, whole blood, urine or tissue. CSF positivity is rare.

- Tissue biopsies for PCR are typically more sensitive in most Lyme patients- cartilage, bladder, gallbladder and cystic duct, small intestine and colon, endometriosis lesions, jaw, fascia and tendons as well as birth organs.

- Bartonella can also be analyzed by DNA probes for tissue presence. Placenta, foreskin, cord segments, colon, heart will often test positive.

Lyme Disease Testing

- Indirect Tests
  - Detection of patient's immune response to *Borrelia burgdorferi*, the causative agent in Lyme disease.
  - Types:
    - Serology (Standard ELISA, C6 peptide)
    - Western Blot
    - Immunofluorescence
- Direct Tests
  - Detection of *Borrelia burgdorferi*-specific proteins (antigens), DNA and RNA, in patient clinical specimen (blood, serum, urine, CSF, etc).
  - Types:
    - Lyme Urine Antigen
    - PCR



Active Lyme Disease

Laboratory support in diagnosis

Why Does IgM Persist?

- Epitope switching.
- Intracellular organism often avoids immune detection.
- Monthly burst out of lymphocytes probably reactivates antibody response.

IgM Antibodies have no ‘memory’. As they are large molecules, they are broken down readily in the liver. IgM antibody represents either new infection or persistent infection.

Laboratory support in diagnosis

The Western Blot

- The Western blot is an entry point to confirmation of diagnosis.
- The IgM Western blot will indicate immune system recognition of and response to the organism within 3-4 months of exposure. In other words, the organism was likely in the blood stream at some point over the last 3-4 months.
- In contrast to common belief expressed in popular medical literature, false positives are quite rare (except for possibly 31 kDa).
- If two or more bands are present, officially 23-25 kDa, (31 kDa), (34 kDa), 39 kDa, 41 kDa, then according to Dr. Burrascano's inclusion criteria there is a likely presence of Lyme disease.
- Unofficially, according to Dr. Charles Ray Jones, if 18 kDa, 23-25 kDa, 30 kDa, 31 kDa, 34 kDa, 37 kDa, 39 kDa, 83 kDa, 93 kDa in any combination or in isolation, the Lyme spirochete is likely present in the individual.

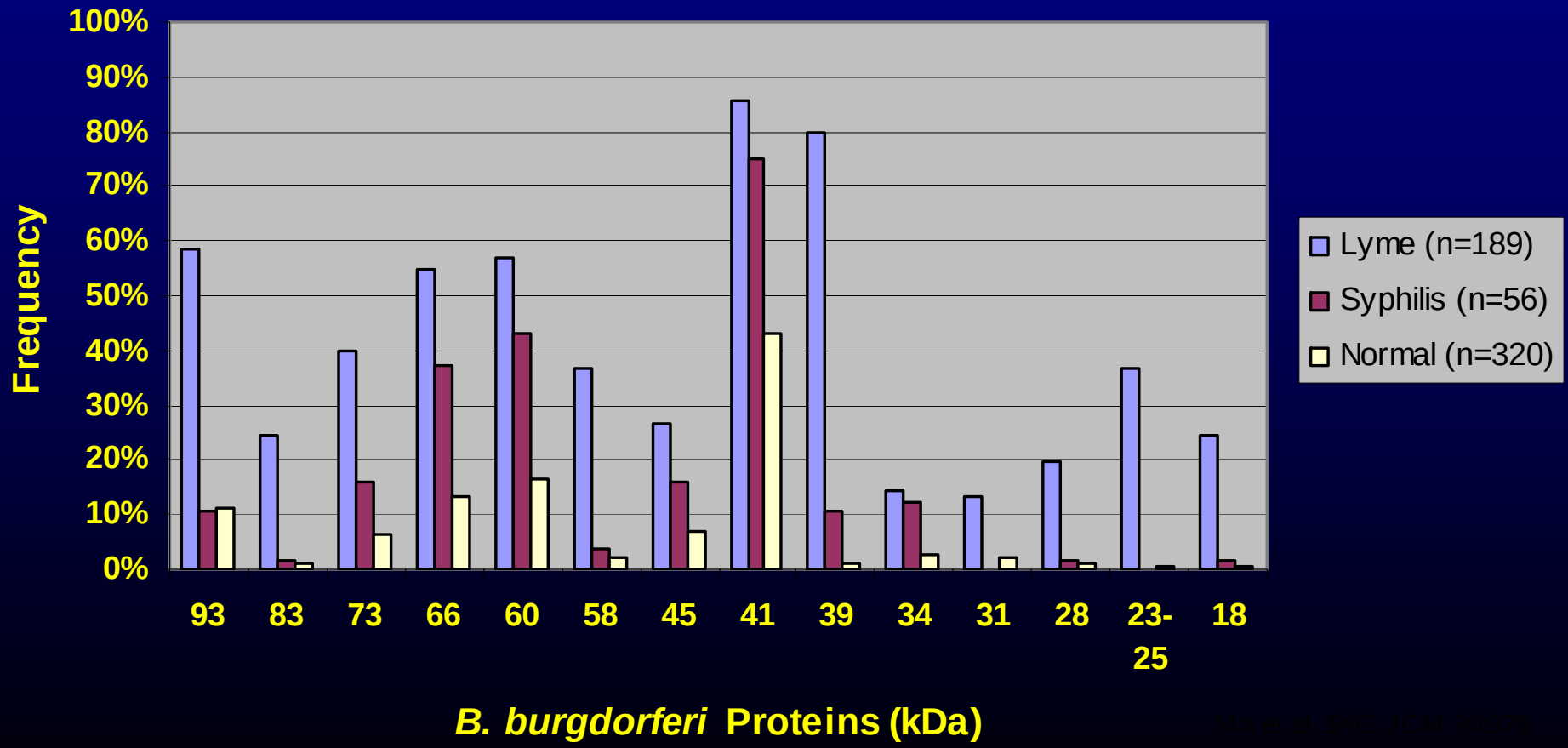
Laboratory support in diagnosis

- Outer surface protein A (Osp A) – 31 kDa
  - A positive band 31 kDa on IgG and/or IgM Western Blot may be a false positive.
  - There is cross-reactivity between *Borrelia* and several viruses.
  - To confirm that a positive band 31kDa is due to *Borrelia*, order the following test from IGeneX, Inc.
    - # 488 – 31 kDa epitope IgM
    - # 489 – 31 kDa epitope IgG
  - I recommend ordering this test only if band 31 kDa is positive in isolation, i.e., no other species-specific bands are positive.

CONTROVERSY
Antibodies of Importance

- 31 kDa (Osp A)
- 34 kDa (Osp B)

Comparison of the Frequency of Antibody Reactivity to Various *B. burgdorferi* Protein Bands Between Lyme Patients, Syphilis and Normal Controls



Ma et al. 1992. JCM 30:376

Shah et. al

- Shah, JS, DuCruz I, Wronska D, Harris S, Harris NS. Comparison of Specificity and Sensitivity of IGeneX Lyme Western Blots Using IGeneX Criteria and CDC Criteria for a Positive Western Blot., Townsend letter, April 2007

- Conclusion
  - IgG 18, 41, and 58 kDa ■
    - Statistically associated with tick-borne diseases
  - IgG 28, 30, 45, 66 kDa
    - Not specific markers for Lyme and other tick-borne diseases
  - IgG and IgM 23-25, 31, 34, 39, 83-93
    - Highly specific markers for Lyme disease

  - Criteria for positive IgM and IgG WB should include bands 23-25, 31, 34, 39, 41, and 83-93

Laboratory support in diagnosis

Many patients will not develop a positive IgG response until the end of disease. If a positive IgG is present it will generally indicate one of several things:

- The patient does not have Lyme disease.
  - Many asymptomatic, healthy partners or siblings of Lyme patients may test positive if their immune system is exposed an/or are warding off a Borrelia infection.
  - One has had the Lyme vaccine.
  - Lab workers, veterinarians, dentists, and hunters.
- One has a healthy immune system and is fighting Bb well.
  - It is a positive predictor of length of time likely required for treatment.

Laboratory support in diagnosis

- One has multiple exposures to several infected ticks and is very sick.
  - These people often come from the East Coast or Europe
- The elderly often mount a brisk IgG response.

Nevertheless, consider the likelihood of Lyme and treat if a clinical diagnosis is made. Don’t treat a test result. Treat a patient

Lyme Disease Case
Classification by CDC

CONFIRMED CASE

A Case with EM, or

A Case of Late Manifestation that is Laboratory Confirmed

Laboratory Confirmation

Isolation of *Borrelia burgdorferi* from a clinical sample or demonstration of IgM or IgG antibodies to *B. burgdorferii* in serum or CSF.

A two-test approach using a sensitive ELISA or IFA, followed by Western Blots.

NOTE: The above is a SURVEILLANCE case definition, developed for national reporting of Lyme Disease by CDC. IT IS NOT INTENDED FOR USE IN CLINICAL DIAGNOSIS.

Ref: MMWR 46:RR10

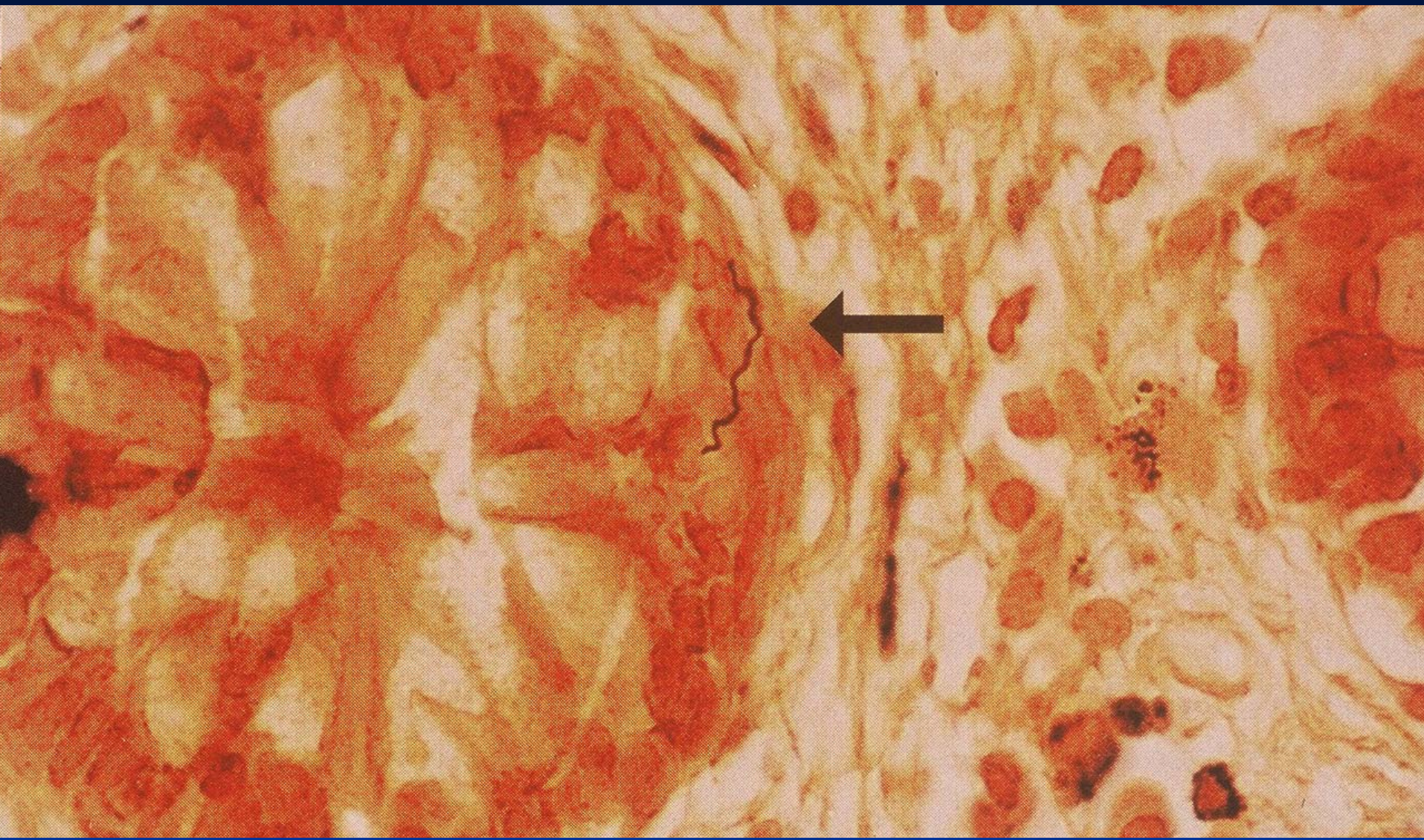
Direct Detection

- Biopsy
- Culture
- Antigen Capture
- Polymerase Chain Reaction (PCR)

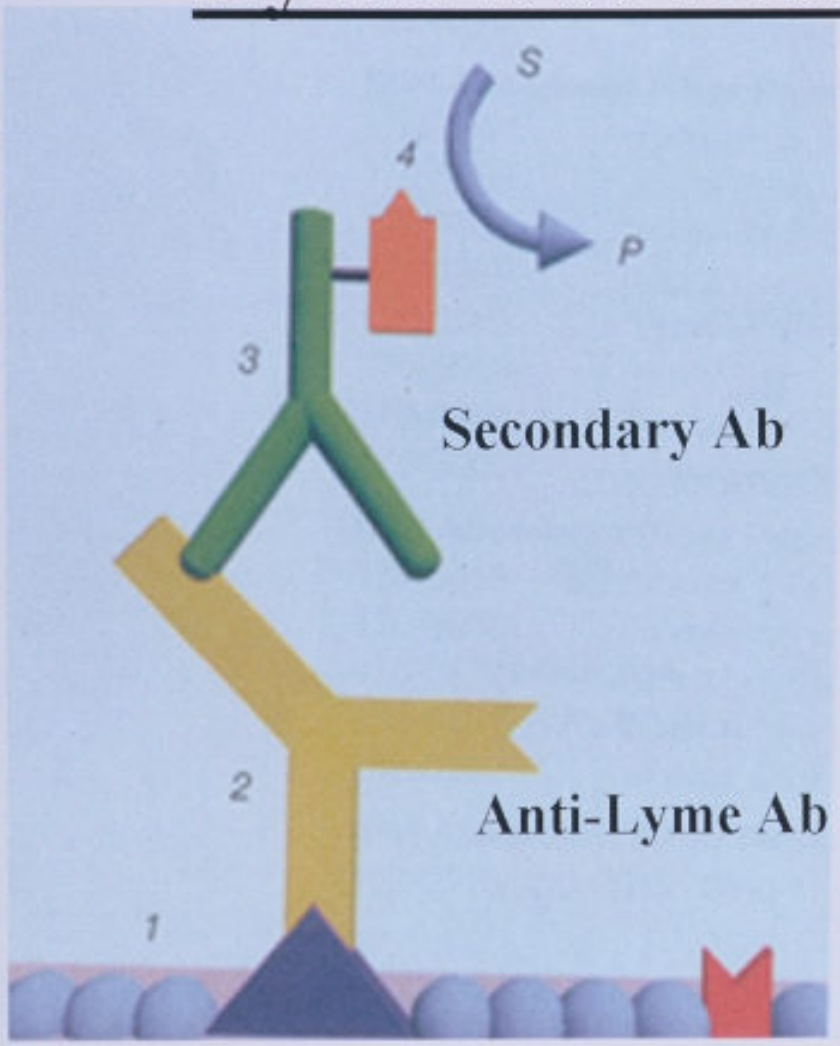
Culture

- Schwan TG. , Burgdorfer W., Schrumpf ME, Karstens RH., 1988. The urinary bladder, a consistent source of B. burgdorferi in experimentally infected white-footed mice. J.Clin Microbiology 26: 893-895.

- Spirochetes more frequently isolated from the bladder (94%) followed by kidney (75%), spleen (61%), blood (13%) and urine (0%).



Lyme Dot-Blot Principle



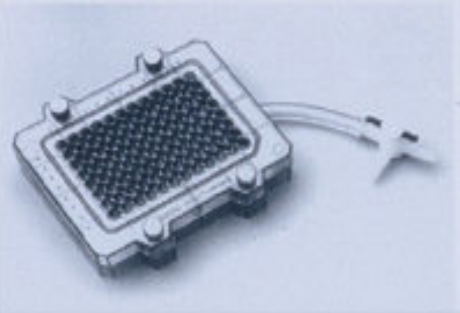
1. Unoccupied sites on the membrane.
2. Primary antibody to a Lyme antigens is incubated with the membrane.
3. Antibody –enzyme conjugate is added to bind to the primary antibody.
4. Color development reagent is added to the blot.
5. The Enzyme converts the substrate (S) to a blue precipitate (P) at the site of the antigen-antibody complex.

→ Lyme antigens in urine bound to membrane

IDEXX

Lyme Dot-Blot Assay

Transfer



Urine

1. Add Lyme Ab
2. Add 2nd Ab
3. Add Sustrate

Results

Blue Dot = Positive

IDEXX

Diagnosis: Induction of a High Yield Lyme Urine DNA and Protein

- If unchallenged serum Western Blot (WB) is negative and high suspicion of Lyme exists → can enhance diagnostic yield of WB without resorting to multi-drug urine challenge and costs associated.
- Give a macrolide x 3 weeks OR doxycycline 100mg bid x 3 weeks.
- On week 4 (four weeks after starting abx, obtain repeat IgM WB. Pay particular attention to 31 kDa and 34 kDa.
- If negative, wait 6-8 weeks before urine induction for protein and DNA.

Some patients may remain seronegative for years.

Diagnosis: Induction of a High Yield Lyme Urine DNA and Protein

- If a patient suspected of Lyme disease has had negative WB and negative whole blood PCR can obtain a higher yield of DNA or protein in the urine by strategically using antibiotics diagnostically.

- Theory:
  - Bb has a life cycle (about 4 months in the helical form). When the bacteria dies, many of its proteins will be shed into the urine. However, given the very low absolute numbers of Bb in the body, randomly testing the urine for pieces of dead bacteria will provide low yield. If one can markedly enhance the amount of dead bacteria being shed, one can maximize likelihood of obtaining a more accurate result.

- Caution: diarrhea, C. difficile, candidiasis, nausea, vomiting, allergy, Stevens-Johnson syndrome, individual drug side effects.

Warn your patients of the risks of using antibiotics in this manner.

Diagnosis: Induction of a High Yield Lyme Urine DNA and Protein

- Many protocols are being used in the US currently by doctors who are members of the International Lyme and Associated Diseases Society (ILADS).

- Protocol 1
  - Day 1: Ceftriaxone 2 grams IV or IM plus Benzathine Penicillin 1.2 million units IM
  - Days 2-5: Clarithromycin 500mg bid or azithromycin 500-600mg qd or doxycycline 100mg tid or minocycline 100mg tid plus cefuroxime 500mg bid or amoxicillin 1000mg tid or cefdinir 300mg bid plus metronidazole 500mg bid or tinidazole 500mg tid
  - Collect first morning urine samples on days 2, 4, and 6

- Protocol 2
  - Days 1-3: ceftriaxone 2 grams IV or IM (May also add azithromycin 500mg qd)
  - Days 2-5: metronidazole 500mg bid or tinidazole 500mg tid
  - Collect first morning urine samples on days 2, 4, and 6

Diagnosis: Induction of a High Yield Lyme Urine DNA and Protein

- Protocol 3 (lower yield, but easier to tolerate)
  - Days 1-7: amoxicillin or cefuroxime or cefdinir plus doxycycline or minocycline or azithromycin or clarithromycin
  - Collect first morning urine samples on days 3, 6, and 8

- Children:
  - Days 1-5: age-weighted dosages for protocol 3 with or without Benzathine or ceftriaxone on day 1
  - Do NOT use doxycycline or minocycline in children < 8 years old
  - Collect first morning urine samples on days 2, 4, and 6

Please have patients use lactobacillus and bifidus +/- saccharomyces to protect GI tract.

If menstruating female, time urine collection with menses.

Laboratory support in diagnosis

Ancillary tests to consider

- Candida Abs
- Arabinatol levels
- EBV (VCA, EA, NA)
- HHV-6
- HHV-7
- Coxsackie
- Parvovirus
- CMV
- HIV
- Mycoplasma pneumoniae
- Vitamin D 25, vitamin D 1,25
- ESR / CRP
- Total CK
- Urine heavy metals
- Stool pathogens
- H. pylori
- Hepatitis panel
- CBC with diff, reticulocytes
- CMP
- CD-57 (HNK-1 panel)
- Thyroid comprehensive panel
- Lipid profile
- Insulin levels
- Glucose tolerance test
- IgG and IgE food antibodies
- HLA typing

Laboratory support in diagnosis

Ancillary tests to consider

- Salivary cortisol
- DHEA
- Sex hormones
- SHBG
- Ferritin
- CEA
- RPR
- Phase 1 and 2 hepatic function
- ABO Rh
- UA
- Urine neurotransmitter
- Organic acids
- Urine amino acids
- Essential elements
- Nutrigenomic testing for methylation cycle
- Fibrinogen / TAT / Soluble fibrin monomer
- Thyroid loading tests
- Mucosal Barrier function
- RNase L activity and protein quantification
- Elastase
- Vitamin deficiencies
- Pregnenolone
- Aldosterone

Laboratory support in diagnosis

Ancillary tests to consider

- HLA typing
- IL-6
- IL-2
- IL-1
- IL-10
- TNF-alpha and 1 betaα
- Coccidioides
- Histoplasma
- Toxoplasma
- Plasma porphyrins
- Ammonia
- Leptin, MSH, VEGF
- ANA with titer, SS-A, SS-B, anti DS DNA, Sm/Rnp AB, complement studies, anti-gliadin, TTG, RF
- Total Immunoglobulin and subclasses
- IgF-1
- Arginine stimulation for HGH
- Plasma amino acids
- Whole blood elements
- Red blood cell elements
- Hair elements
- KPU
- Serum minerals
- Zinc, copper, magnesium

Treating Lyme disease

- The basics of treating Lyme can be found in “Diagnostic Hints and Treatment Guidelines for Lyme and Other Tick Borne Illnesses” by Joseph Burrascano Jr, MD.
- Generally you can start fast and furious or slow and steady. Some patients do well with a quick aggressive treatment. Many doctors have tremendous success in the more hearty patients. Other patients may unexpectedly become quite sick 2-4 days after starting or even at 21-28 days after treatment begins.
- This is usually due to a Jarisch-Herxheimer reaction, in which a torrent of cytokines and toxins spill into the body humors.
- Symptoms can range from worsening fatigue, joint pain or swelling and dysuria to shock, coma and death.
- You may have to “play catch-up” for months.

Treating Lyme disease

Some conditions that I recommend not be treated too aggressively at first:

- Severe neurological conditions
- Baseline abdominal distress
- Chemically sensitive individuals
- Children
- The elderly
- If one suspects but does not know co-infection status
- Women with pelvic pain or frequent headaches
- In severe early Lyme, aggressive therapy is generally well tolerated.

Aggressive therapy defined:

- IV medications
- High dose antibiotic combinations
- Flagyl or tinidazole and a high dose anti-spiral medicine.

Two very different standards of care

- New England Journal of Medicine article states “Chronic Lyme disease, which is equated with chronic B. burgdorferi infection, is a misnomer, and the use of prolonged, dangerous and expensive antibiotic treatments for it is not warranted” (Feder et. Al)
- IDSA 2006 guidelines for the diagnosis and treatment of Lyme disease
- AAN guidelines; independent corroboration?
- “Prolonged Lyme disease treatment” (Halperin, Journal Neurology)

VS

- A randomized, placebo-controlled trial of repeated IV antibiotic therapy for Lyme encephalopathy (Fallon et al, Journal Neurology)
- ILADS guidelines for the diagnosis and treatment of Lyme disease
- Lyme disease: a turning point (Stricker and Johnson, Future drugs)
- Treatment of Lyme disease: a medicolegal assessment (Johnson and Stricker, Future drugs)

Evidence-Based Guidelines for the Management of Lyme Disease

- Since there is currently no definitive test for Lyme disease, laboratory results should not be used to exclude an individual from treatment.
- Lyme disease is a clinical diagnosis and tests should be used to support rather than supersede the physician's judgment.
- The early use of antibiotics can prevent persistent, recurrent and refractory Lyme disease.
- The duration of therapy should be guided by clinical response, rather than by an arbitrary (i.e., 30 day) treatment course.
- The practice of stopping antibiotics to allow for delayed recovery is not recommended for persistent Lyme disease. In these cases, it is reasonable to continue treatment for several months after clinical and laboratory abnormalities have begun to resolve and symptoms have disappeared.

Expert Rev Antiinfect Ther 2004;2(1 Suppl):S1-13

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Treatment of Chronic Lyme

What should one start with?

- Doxycycline 100mg tid or minocycline 100mg bid is a good first choice. Use for 6 weeks before considering adding a second agent or starting parenteral therapy
- Alternatively, may start with cefdinir 300mg bid-tid or cefuroxime 500mg bid-tid or amoxicillin 875mg tid
- After 3-8 weeks, may increase dose or add a second agent

Become comfortable with a few antibiotics. Know their side effect profiles. Consider increasing the dose before adding a second agent.

Treatment of Chronic Lyme

What should one start with?

- The second agent should be of a different class and work by a different mechanism.
- Azithromycin 500 - 600mg qd or clarithromycin 500mg bid is often a good choice if first medicine is a beta-lactam antibiotic.
- While the tetracyclines and the macrolides are both ribosomal inhibitors and often not used in combination, in actual practice, this combination has proven quite effective for Lyme.

When choosing an antibiotic think about intracellular activity, central nervous system penetration, bactericidal vs bacteriostatic activity and likelihood of patient compliance. Know how much each medicine costs.

Treatment of Chronic Lyme

What should one start with?

- Recommend against using macrolides as monotherapy for more than 4 weeks due to possible resistance.
- Benzathine PCN 1.2 million units 2-3x/week is a good adjunctive treatment as it has good CNS penetration.
- Metronidazole/Tinidazole is useful as pulse therapy 2-3 months at a time. Do not use without a cell wall-active drug.
- Many ILADS doctors recommend treating two months past the resolution of active symptoms. This can take more than a year.

Treatment of Chronic Lyme

What should one start with?

- Most patients with severe chronic persistent neuroborreliosis will require parenteral therapy. Recommend oral meds for 3-4 months prior to starting IV or IM.

- Parenteral drug of choice is Ceftriaxone 2 grams qd-bid 4-7 days a week.

- Cefotaxime 2 grams tid or Ampicillin 2-4grams tid-qid is also effective.

Ceftriaxone is not a miracle drug. Very ill patients may be on this for more than one year. It should be used with an intracellular oral drug for at least part of the treatment. Also one should use ursodiol with Ceftriaxone to protect gallbladder.

Treating Lyme disease

I ramp up most patients slowly, maintaining them on two or more medications.

- Prescribe one or more intracellular acting drugs (doxy, mino, macrolides, ketolide, rifampin, quinolones, sulfa.
- A cell wall (B-lactam) antibiotic (PCN, cephalosporin, carbapenem, vancomycin).
- A cyst buster (metronidazole, tinidazole, nitrosoxamide, hydroxychloroquine).
- The problem is tolerance. One has to tread a fine line. A great regimen could be Ketek, doxycycline, Omnicef and metronidazole were it not so toxic and the poor interaction between doxycycline and metronidazole.
- A more realistic approach would be to change combinations regularly (q 6-12 weeks) to affect different properties of the organism.

Advanced antibiotic strategies

- After a patient has had 6-8 months of ceftriaxone or similar drug, the options for care become more complex.

- If a patient has had an IV cell wall drug with or without an intracellular and a cyst buster, I would often add IV azithromycin (500mg over 2-3 hours) or doxycycline (400 mg bolus over 3 hours). In addition I might use Imipenem, meropenem, or ertapenem (Invanz) instead of the cephalosporin. After 3-6 weeks one could switch one of the drugs for IV Flagyl. Later one might consider Zosyn or Tygacil, pulsed for 3-4 weeks.

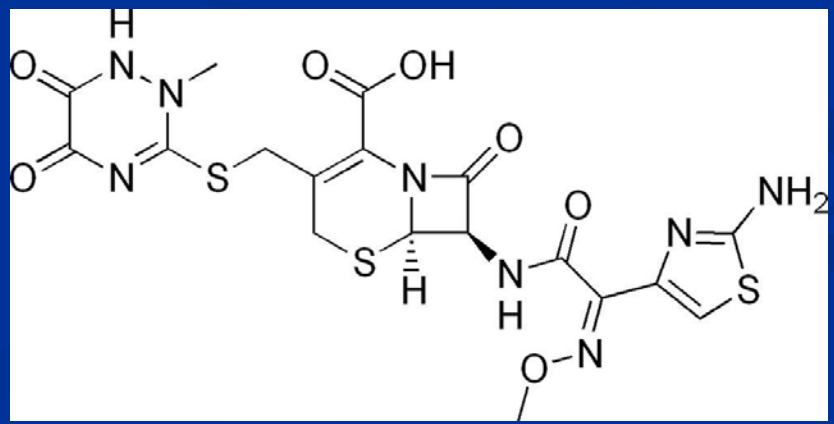
- If co-infections have already been treated with standard orals, can rotate IV levofloxacin, moxifloxacin, clindamycin or IV rifampin.

- Many herbal protocols can be used in addition.

Intravenous Antibiotics

Ceftriaxone (Rocephin)

- Pharmacologic Category
  - Cephalosporin (3rd generation)
- Empirical Formula
  - $C_{18}H_{18}N_8O_7S_3$
- Structural Formula



Ceftriaxone (Rocephin)

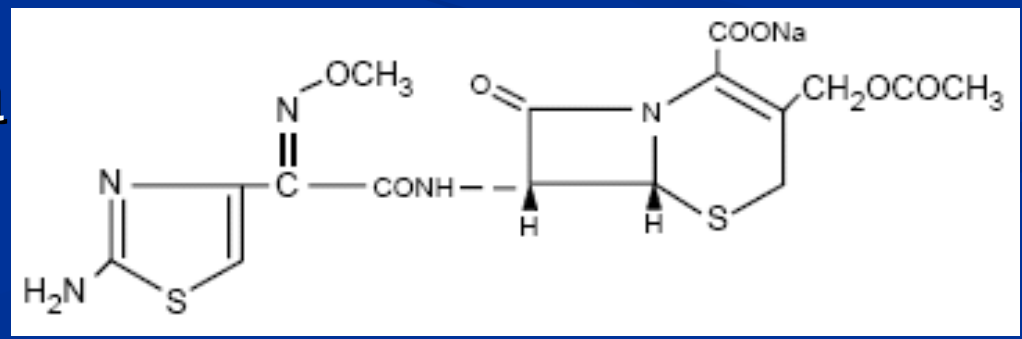
- Mechanism of Action
  - Bactericidal
  - Inhibits bacterial cell wall synthesis
    - Binds to one or more of the penicillin-binding proteins (PBPs)
    - Inhibits final transpeptidation step of peptidoglycan synthesis in bacterial cell walls
    - Inhibits cell wall biosynthesis
    - Bacteria eventually lyse due to ongoing activity of cell wall autolytic enzymes while cell wall assembly is arrested
- Dosage
  - 2 grams IM qd, 4-5 days a week
  - 2 grams IV qd, 7 days a week
  - 2 grams IV bid, 4 days a week

Ceftriaxone (Rocephin)

- Warnings/Precautions
  - Gallbladder disease
  - Precipitation caused by calcium-containing products
- Prescribing Information
  - http://www.gene.com/gene/products/information/rocephin/pdf/pi.pdf

Cefotaxime (Claforan)

- Pharmacologic Category
  - Cephalosporins
- Empirical Formula
  - $C_{16}H_{16}N_5NaO_7S_2$
- Structural Formula



Cefotaxime (Claforan)

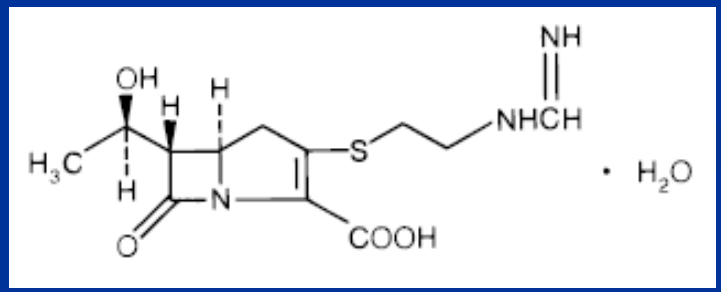
- Mechanism of Action
  - Bactericidal
  - Inhibits cell well synthesis
- Dosage
  - 2 grams IV q8h

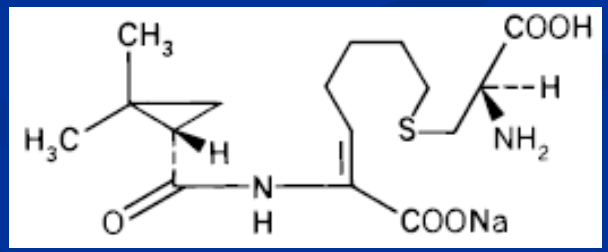
Cefotaxime (Claforan)

- Warnings/Precautions
  - Most frequent adverse reactions include CNS (0.2%), GI (1.7%), GU (<1%), Hematologic (<1%)
- Prescribing Information
  - http://products.sanofi-aventis.us/claforan/claforan.pdf

Imipenem/Cilastatin (Primaxin)

- Pharmacologic Category
  - Carbapenems
- Empirical Formula
  - $C_{12}H_{17}N_3O_4S \cdot H_2O$ / $C_{16}H_{25}N_2O_5SNa$
- Structural Formula





Imipenem/Cilastatin (Primaxin)

- Mechanism of Action
  - Bactericidal
  - Inhibits cell wall synthesis
- Dosage
  - 1 gram IV q12h

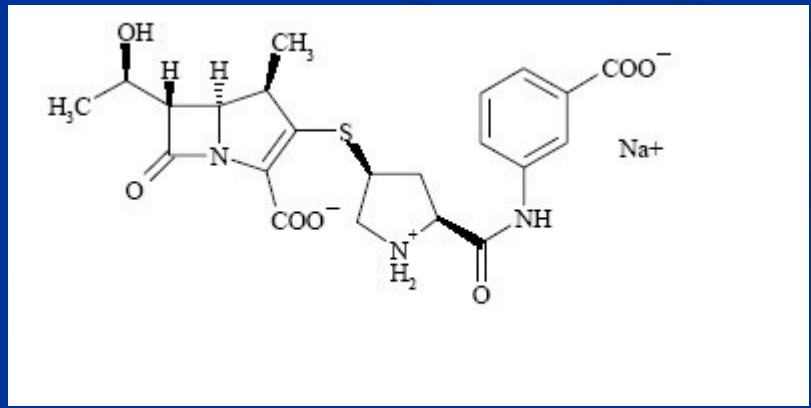
Imipenem/Cilastatin (Primaxin)

- Warnings/Precautions
  - Most frequently reported systemic adverse reactions were nausea (2%), diarrhea (1.8%), vomiting (1.5%), rash (0.9%), fever (0.5%), hypotension (0.4%), seizures (0.4%), dizziness (0.3%), pruritis (0.3%), urticaria (0.2%), somnolence (0.2%)

- Prescribing Information
  - http://www.merck.com/product/usa/pi_circulars/p/primaxin/primaxin_iv_pi.pdf

Ertapenem (Invanz)

- Pharmacologic Category
  - Carbapenems
- Empirical Formula
  - $C_{22}H_{24}N_3O_7SNa$
- Structural Formula



Ertapenem (Invanz)

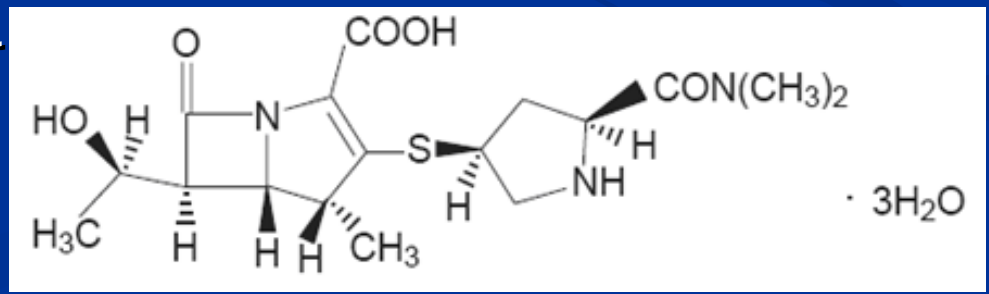
- Mechanism of Action
  - Bactericidal
  - Inhibits cell wall synthesis
- Dosage
  - 1 gram IM qd
  - 1 gram IV qd

Ertapenem (Invanz)

- Warnings/Precautions
  - Most common adverse reactions were diarrhea (5.5%), infused vein complication (3.7%), nausea (3.1%), headache (2.2%), vaginitis in females (2.1%), phlebitis/thrombophlebitis (1.3%) and vomiting (1.1%)
- Prescribing Information
  - http://www.merck.com/product/usa/pi_circulars/i/invanz/invanz_pi.pdf

Meropenem (Merrem)

- Pharmacologic Category
  - Carbapenems
- Empirical Formula
  - $C_{17}H_{25}N_3O_5S \cdot 3H_2O$
- Structural Formula



Meropenem (Merrem)

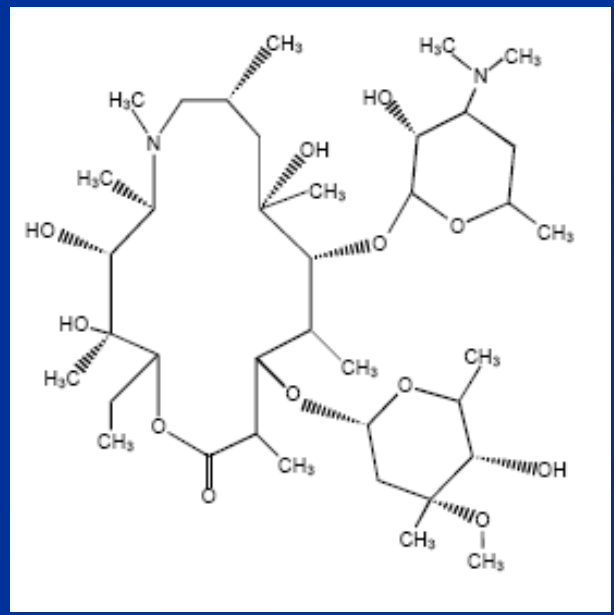
- Mechanism of Action
  - Bactericidal
  - Inhibits cell wall synthesis
    - Penetrates bacterial cells readily and interferes with the synthesis of vital cell wall components, leading to cell death
- Dosage
  - 2 grams IV q8h

Meropenem (Merrem)

- Warnings/Precautions
  - Most common systemic adverse reactions include diarrhea (4.8%), nausea/vomiting (3.6%), headache (2.3%), rash (1.9%), sepsis (1.6%), constipation (1.4%), apnea (1.3%), shock (1.2%), and pruritis (1.2%)
- Prescribing Information
  - http://www1.astrazeneca-us.com/pi/MerremIV.pdf

Azithromycin (Zithromax)

- Pharmacologic Category
  - Macrolides
- Empirical Formula
  - $C_{38}H_{72}N_2O_{12}$
- Structural Formula



Azithromycin (Zithromax)

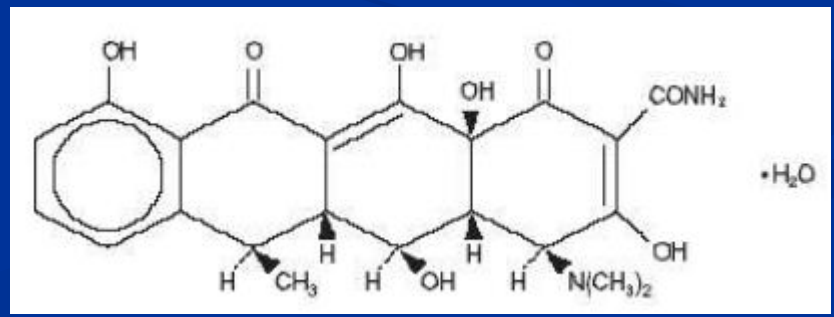
- Mechanism of Action
  - Bacteriostatic
  - Inhibits protein synthesis
    - Binds to the 50S ribosomal subunit and inhibits translocation of the peptidyl tRNA from the A to the P site
  - Nucleic acid synthesis is not affected
- Dosage
  - 500 mg IV qd, 5-7 days a week

Azithromycin (Zithromax)

- Warnings/Precautions
  - Most common adverse reactions include diarrhea, nausea, abdominal pain, vomiting, anorexia, rash, pruritis
- Prescribing Information
  - http://www.pfizer.com/files/products/uspi_zithromaxIV.pdf

Doxycycline (Vibramycin)

- Pharmacologic Category
  - Tetracycline
- Empirical Formula
  - $(C_{22}H_{24}N_2O_8 \cdot HCl)_2 \cdot C_2H_5O \cdot H_2O$
- Structural Formula



Doxycycline (Vibramycin)

- Mechanism of Action
  - Bacteriostatic
  - Inhibits protein synthesis
    - Reversibly binds to the 30S ribosomal subunit and inhibits binding of aminoacyl tRNA to the acceptor site on the 70S ribosome
- Dosage
  - 300-400mg IV qd

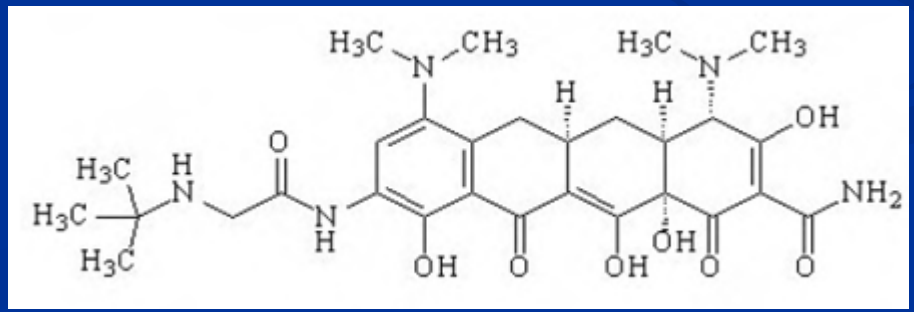
Doxycycline (Vibramycin)

- Warnings/Precautions
  - Caution against dental discoloration and sun sensitivity
  - Side effects include diarrhea, loss of appetite, nausea, vomiting, headache, rectal discomfort

- Prescribing Information
  - http://www.bedfordlabs.com/products/inserts/Div-DCY-P03.pdf

Tigecycline (Tygacil)

- Pharmacologic Category
  - Glycylcyclines
    - semi-synthetic derivatives of tetracycline with a glycylamido moiety attached at the 9 position of the D-ring of the base molecule
- Empirical Formula
  - $C_{29}H_{39}N_5O_8$
- Structural Formula



Tigecycline (Tygacil)

- Mechanism of Action
  - Inhibits protein translation
    - Binds to the 30S ribosomal subunit and blocks entry of amino-acyl tRNA molecules into the A site of the ribosome
    - This prevents incorporation of amino acid residues into elongating peptide chains
- Dosage
  - 50mg IV q12h

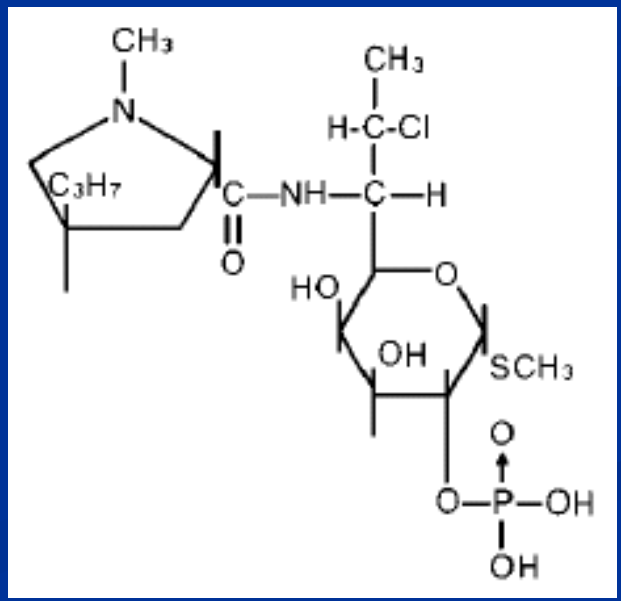
Tigecycline (Tygacil)

- Warnings/Precautions
  - Most common adverse reactions include nausea, vomiting, diarrhea, abdominal pain, headache, and increased SGPT

- Prescribing Information
  - http://www.pfizerpro.com/content/showlabeling.asp?id=491

Clindamycin (Cleocin)

- Pharmacologic Category
  - Lincosamides
- Empirical Formula
  - $C_{18}H_{34}ClN_2O_8PS$
- Structural Formula



Clindamycin (Cleocin)

- Mechanism of Action
  - Bacteriostatic
  - Inhibits bacterial protein synthesis
    - Inhibits ribosomal translocation by binding preferentially to the 23S rRNA of the large bacterial ribosome subunit
- Dosage
  - 600mg IV q8h

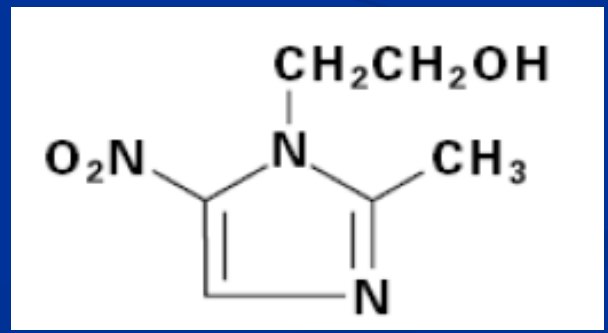
Clindamycin (Cleocin)

- Warnings/Precautions
  - *Clostridium difficile* associated diarrhea!

- Prescribing Information
  - http://www.pfizer.com/files/products/uspi_cleocin_phosphate.pdf

Metronidazole (Flagyl)

- Pharmacologic Category
  - Nitroimidazole
- Empirical Formula
  - $C_6H_9N_3O_3$
- Structural Formula



Metronidazole (Flagyl)

- Mechanism of Action
  - Inhibits nucleic acid synthesis
    - Disrupts the DNA's helical structure resulting in bacterial cell death
- Dosage
  - 500mg IV q12h

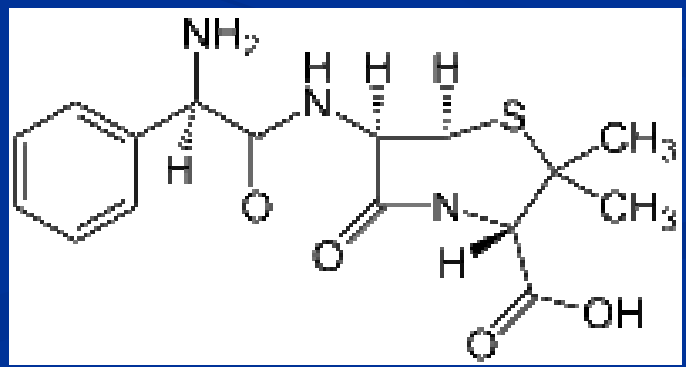
Metronidazole (Flagyl)

- Warnings/Precautions
  - Avoid alcoholic beverages
  - Most common adverse reactions include nausea, sometimes accompanied by headache, anorexia, and occasionally vomiting; diarrhea; epigastric distress; and abdominal cramping

- Prescribing Information
  - http://www.pfizer.com/files/products/uspi_flagyl.pdf

Ampicillin

- Pharmacologic Category
  - Penicillin
- Empirical Formula
  - $C_{16}H_{19}N_3O_4S$
- Structural Formula



Ampicillin

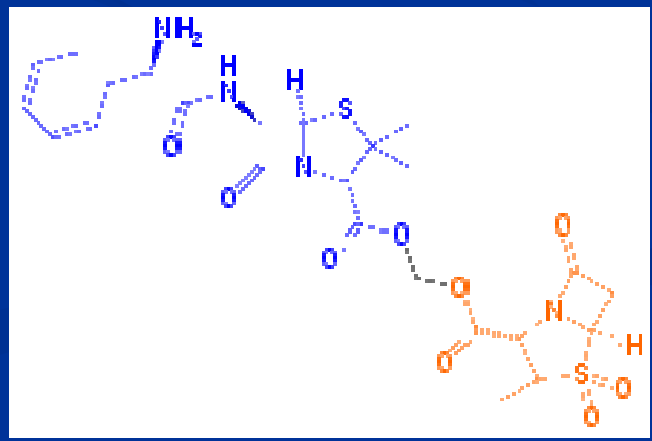
- Mechanism of Action
  - Bactericidal
  - Inhibits cell wall synthesis
    -
- Dosage

Ampicillin

- Warnings/Precautions
  - Do not administer in patients with mononucleosis
- Prescribing Information
  - http://www.sagentpharma.com/Products/Ampicillin/Catalog/Ampicillin_PI1.pdf

Ampicillin/Sulbactam (Unasyn)

- Pharmacologic Category
  - Penicillin + β-lactamase inhibitor
- Empirical Formula
  - $C_{16}H_{18}N_3NaO_4S$ / $C_8H_{10}NNaO_5S$
- Structural Formula



Ampicillin/Sulbactam (Unasyn)

- Mechanism of Action
  - Bactericidal
  - Ampicillin inhibits cell wall mucopeptide biosynthesis
  - Sulbactam inhibits beta-lactamases, allowing ampicillin to attack and kill the bacteria

- Dosage

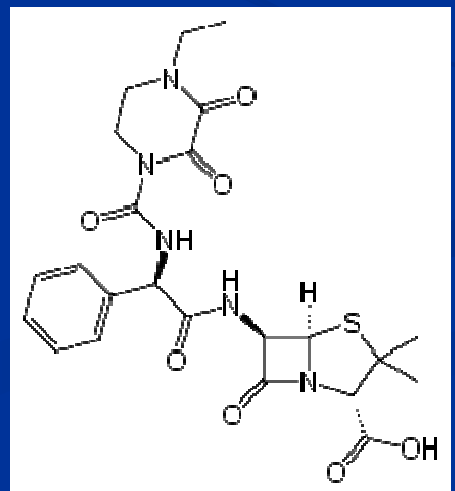
Ampicillin/Sulbactam (Unasyn)

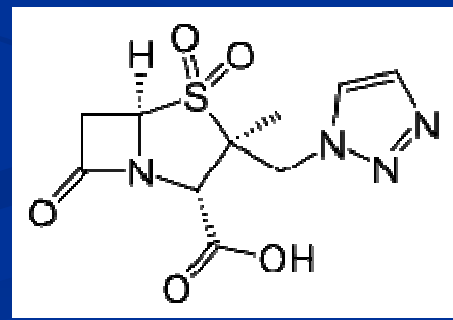
- Warnings/Precautions
  - Do not administer in patients with mononucleosis
  - Most common systemic reactions are diarrhea (3%) and rash (<2%).

- Prescribing Information
  - http://www.pfizer.com/files/products/uspi_unasyn.pdf

Piperacillin/Tazobactam (Zosyn)

- Pharmacologic Category
  - Penicillin + β-lactamase inhibitor
- Empirical Formula
  - $C_{23}H_{26}N_5NaO_7S$ / $C_{10}H_{11}N_4NaO_5S$
- Structural Formula





Piperacillin/Tazobactam (Zosyn)

- Mechanism of Action
  - Bactericidal
  - Piperacillin inhibits septum formation and cell wall synthesis
  - Tazobactam inhibits beta-lactamases
- Dosage

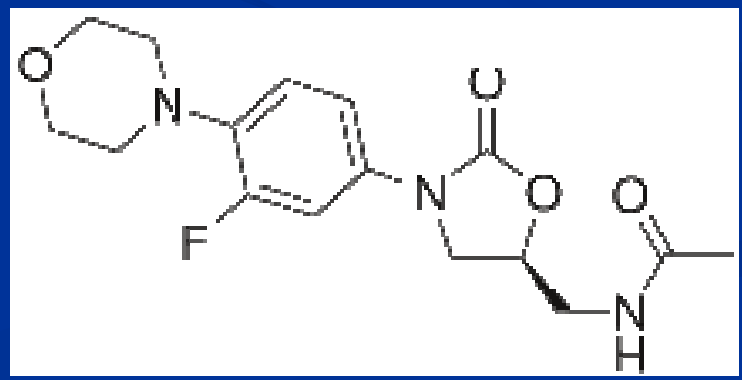
Piperacillin/Tazobactam (Zosyn)

- Warnings/Precautions
  - Most common adverse reactions include diarrhea, headache, constipation, nausea, insomnia, rash, vomiting, dyspepsia, pruritis, stool changes, fever, agitation, pain, moniliasis, hypertension, dizziness, abdominal pain, chest pain, edema, anxiety, rhinitis, and dyspnea.

- Prescribing Information
  - http://www.pfizerpro.com/content/showlabeling.asp?id=477

Linezolid (Zyvox)

- Pharmacologic Category
  - Oxazolidinone
- Empirical Formula
  - $C_{16}H_{20}FN_3O_4$
- Structural Formula



Linezolid (Zyvox)

- Mechanism of Action
  - Binds to a site on the bacterial 23S ribosomal RNA of the 50S subunit and prevents the formation of a functional 70S initiation complex, which is an essential component of the bacterial translation process
- Dosage

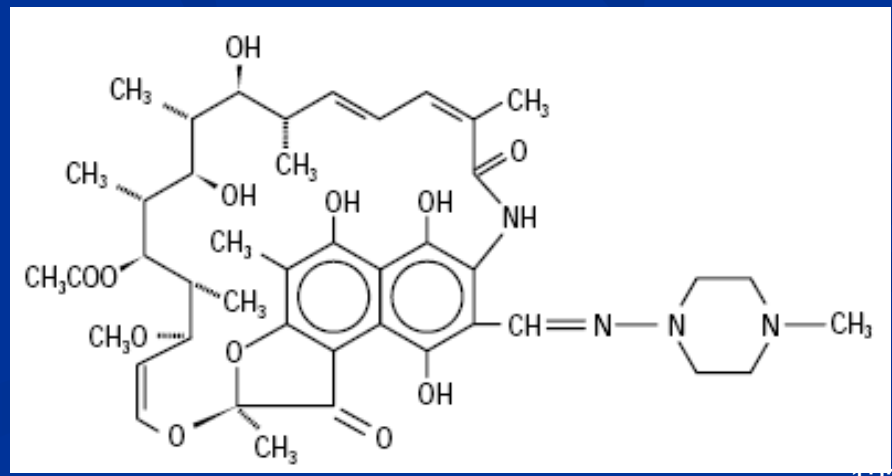
Linezolid (Zyvox)

- Warnings/Precautions
  - Myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia) and lactic acidosis have been reported
  - Monitor weekly CBCs
  - Most common adverse reactions include diarrhea (2.8%-11%), headache (0.5%-11.3%) and nausea (3.4%-9.6%)

- Prescribing Information
  - http://media.pfizer.com/files/products/uspi_zyvox.pdf

Rifampin (Rifadin)

- Pharmacologic Category
  - Derivative of rifamycin
- Empirical Formula
  - $C_{43}H_{58}N_4O_{12}$
- Structural Formula



Rifampin (Rifadin)

- Mechanism of Action
  - Inhibits RNA synthesis
    - Blocks RNA transcription
- Dosage
  - 600mg IV qd

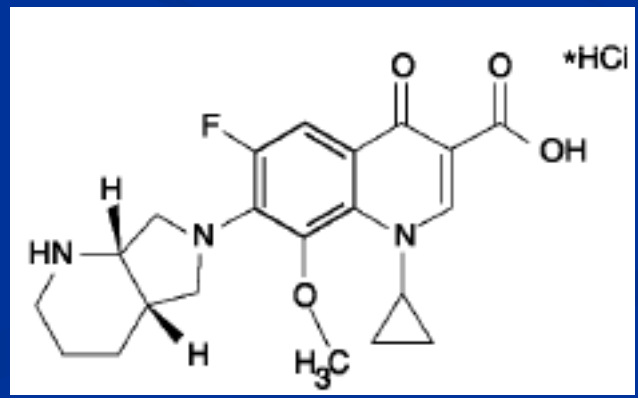
Rifampin (Rifadin)

- Warnings/Precautions
  - Can enhance metabolism of endogenous substrates, including adrenal hormone, thyroid hormones, and vitamin D
  - Can elevate sex hormone binding globulin
  - Can produce a reddish coloration of bodily fluids
  - Many drug-drug interactions

- Prescribing Information
  - http://products.sanofi-aventis.us/rifadin/Rifadin.pdf

Moxifloxacin (Avelox)

- Pharmacologic Category
  - Quinolones
- Empirical Formula
  - $C_{21}H_{24}FN_3O_4$
- Structural Formula



Moxifloxacin (Avelox)

- Mechanism of Action
  - Bactericidal
  - Inhibits topoisomerase II (DNA gyrase) and topoisomerase IV required for bacterial DNA replication, transcription, repair, and recombination.
  - MOA is different from that of macrolides, beta-lactams, aminoglycosides, or tetracyclines

- Dosage
  - 400mg IV qd

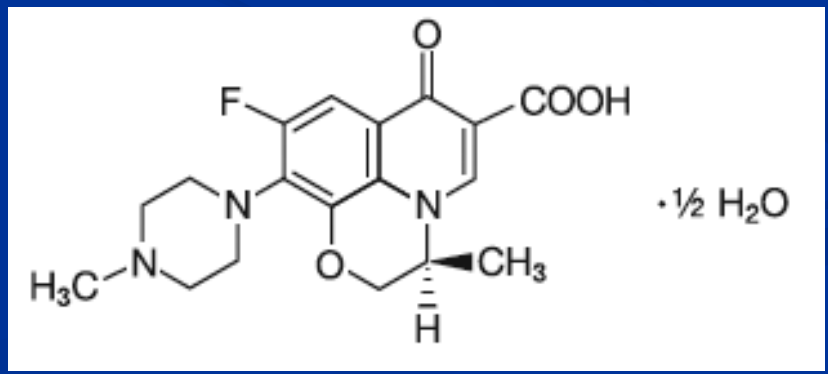
Moxifloxacin (Avelox)

- Warnings/Precautions
  - Increased risk of tendinitis and tendon rupture
  - May produce changes in an electrocardiogram (QTc interval prolongation)
  - Most common adverse reactions include nausea (6%), diarrhea (5%), and dizziness (2%)

- Prescribing Information
  - http://www.avelox.com/html/pdf/avelox_prescribing.pdf

Levofloxacin (Levaquin)

- Pharmacologic Category
  - Quinolones
- Empirical Formula
  - $C_{18}H_{20}FN_3O_4$
- Structural Formula



Levofloxacin (Levaquin)

- Mechanism of Action
  - Inhibits bacterial topoisomerase IV and DNA gyrase (both of which are type II topoisomerases), enzymes required for DNA replication, transcription, repair and recombination
  - MOA is different from that of aminoglycosides, macrolides, and beta-lactams

- Dosage
  - 500mg IV qd

Levofloxacin (Levaquin)

- Warnings/Precautions
  - Increased risk of tendinitis and tendon rupture
  - Most common adverse reactions include nausea, headache, diarrhea, insomnia, constipation, and dizziness

- Prescribing Information
  - http://www.levaquin.com/sites/default/files/pdf/levaquin.pdf#zoom=100

Case # 1 (JR)

[redacted]

Perscription Medicatoins List

* Short course - 10 Days

Current Perscription Medications:

Brand Name	Generic Name	Concentration	Dosage	Frequency
BEG Coumpound Spray	EDTA + Gentamycin + Mpirocin		2 sprays	4/day
Cephalexin*	Cephalexin		500mg	4/day
Desyrel	Trazodone		50 mg	1/day
Heparin Inj.	Heparin Inj.	10,000 U/ml	1/2 ml	1/day
Miralax (Glycolax)	Polyethylene Glycol 3350		17 g	2/day
Rifadin	Rifampin		600 mg	1/day
Tindamax	Tinidazole		500mg	4/day
Testosterone	Testosterone Cypionate	200 mg/ml	0.25 ml	1/week
Westhroid	Desicated Thyroid		40 mg	1/day
Zithromax (Oral)	Azithromycin		500 mg	1/day

IV Supplies:

Heparin Flush		100 U/ml	10 ml	1/infusion
Saline bags		0.90%	500 ml	1/infusion
Saline Flush		0.90%	10 ml	2/infusion

Moly•B 1 tab
Bromelain 4 Cap 4 Cap

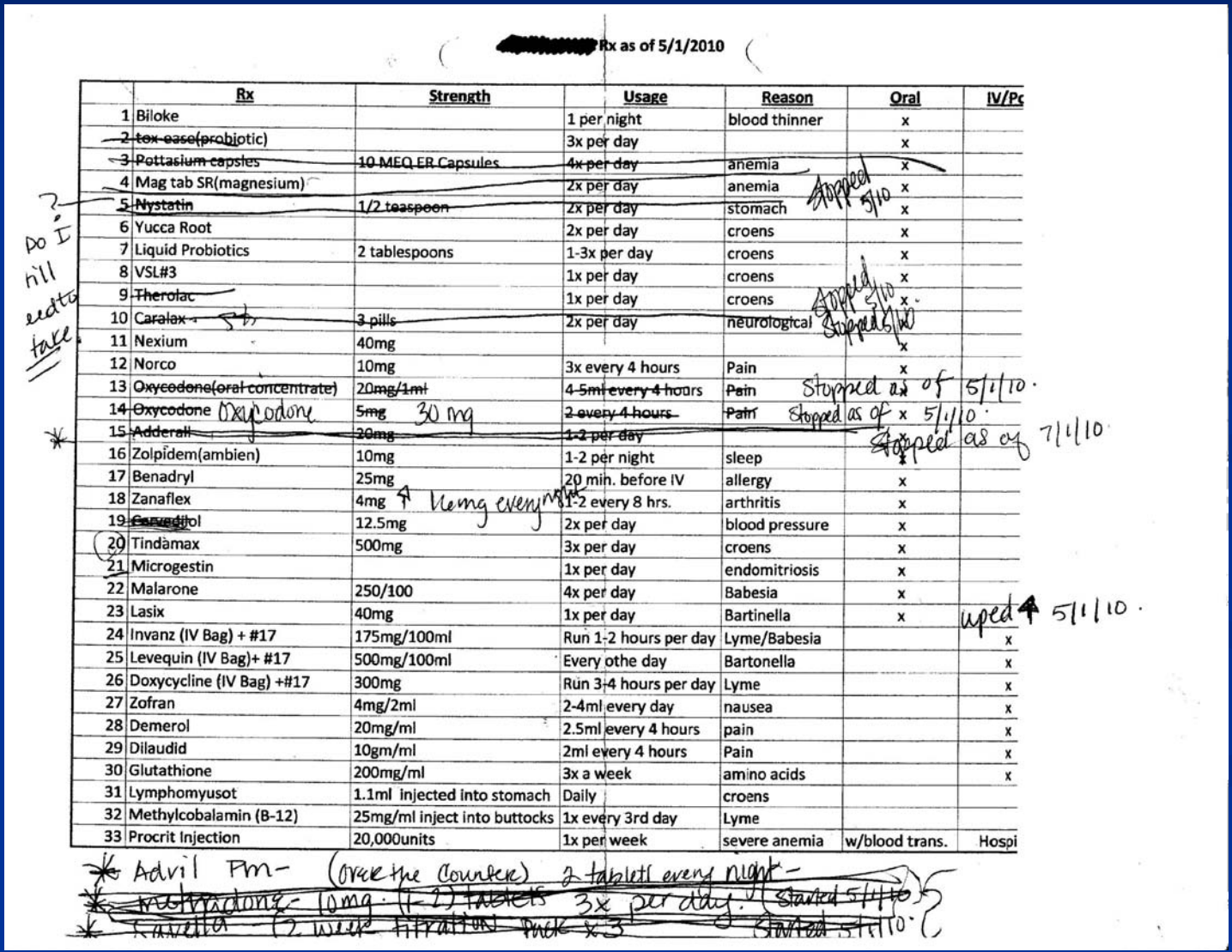
Name: [redacted] Date: [redacted]

According to the 9th Amendment of the U.S. Constitution, you retain the right of choice in health care. Subsequent to your Laboratory and/or Auronomic Response Testing assessments, the following protocol is suggested. It is not intended as diagnosis, prescription, treatment or cure for any disease. Dependence is being placed on education, counselling, naturopathic modalities and natural substances in an effort to help stimulate and maintain your intrinsic self-healing processes. These modalities may include foods, food extracts, botanical substances, digestive aids, vitamins, minerals, enzymes, and the purchase and use of any therapy regimen, remedy or product. It is solely your decision and responsibility to follow any suggestions offered.

Continue on this program until your next appointment at which time they will be re-evaluated.

Supplement	Empty Stomach	with Breakfast	Empty Stomach (10-11 am)	with Lunch	Empty Stomach (2-3 pm)	with Dinner	Bedtime
Zithro (Oral)? Rifampin IV, Tindamax 1000(2x), Finish Beg.							
Westhroid, Testosterone, Heparin, Trazodone, Nystatin (1pill/meal)							
CSM	X				X		
Hydroxy B12		2drops					
Readisorb MB12		1 spray (2x/wk)					
Protifolate		¼ tab					
Vit D 400		4drops					
The Core							3 caps
Destroxio		3caps		3caps		3caps	
TRiguard		1 cap		1cap		1cap	
TF Plus Myc							
Release		2caps		2caps		2caps	
Bromoke	2caps				2caps		
Bar-1		→15drops		→15drops		→15drops	
Immunotia (slowly!)		→15		→15		→15	
L Drain	2dropperfuls/day						
K Drain	1dropperful/day						
Lymphomyosot	1 ampoule everyday (inject)						
Red Root		30drops				30drops	
Sacc DF.		2caps				2caps	
VSL#3							2caps
My Rizol		→15drops				→15drops	
Iwa Flush every		4-6 wks (not at fullmoons)					
Iwa Red							
Sauna							
Bar-1 on foot							
Electrolytes							

Case # 2 (JS)



[redacted] Rx as of 5/1/2010

	Rx	Strength	Usage	Reason	Oral	IV/Pc
1	Biloke		1 per night	blood thinner	x	
2	~~tox-ease(probiotic)~~		3x per day		x	
3	~~Pottasium capsles~~	~~10 MEQ ER Capsules~~	~~4x per day~~	anemia	x	
4	Mag tab SR(magnesium)		2x per day	anemia	x	
5	~~Nystatin~~	~~1/2 teaspoon~~	~~2x per day~~	stomach	x	
6	Yucca Root		2x per day	croens	x	
7	Liquid Probiotics	2 tablespoons	1-3x per day	croens	x	
8	VSL#3		1x per day	croens	x	
9	~~Therolac~~		1x per day	croens	x	
10	~~Caralax~~	~~3 pills~~	~~2x per day~~	neurological	x	
11	Nexium	40mg			x	
12	Norco	10mg	3x every 4 hours	Pain	x	
13	~~Oxycodone(oral concentrate)~~	~~20mg/1ml~~	~~4-5ml every 4 hours~~	~~Pain~~	x	
14	~~Oxycodone~~ Oxycodone	~~5mg~~ 30 mg	~~2 every 4 hours~~	~~Pain~~	x	
15	~~Adderall~~	~~20mg~~	~~1-2 per day~~		x	
16	Zolpidem(ambien)	10mg	1-2 per night	sleep	x	
17	Benadryl	25mg	20 min. before IV	allergy	x	
18	Zanaflex	4mg 4 4mg every 8 hrs	1-2 every 8 hrs.	arthritis	x	
19	~~Carvedilol~~	12.5mg	2x per day	blood pressure	x	
20	Tindamax	500mg	3x per day	croens	x	
21	Microgestin		1x per day	endomitriosis	x	
22	Malarone	250/100	4x per day	Babesia	x	
23	Lasix	40mg	1x per day	Bartinella	x	
24	Invanz (IV Bag) + #17	175mg/100ml	Run 1-2 hours per day	Lyme/Babesia		x
25	Levequin (IV Bag)+ #17	500mg/100ml	Every othe day	Bartonella		x
26	Doxycycline (IV Bag) +#17	300mg	Run 3-4 hours per day	Lyme		x
27	Zofran	4mg/2ml	2-4ml every day	nausea		x
28	Demerol	20mg/ml	2.5ml every 4 hours	pain		x
29	Dilaudid	10gm/ml	2ml every 4 hours	Pain		x
30	Glutathione	200mg/ml	3x a week	amino acids		x
31	Lymphomyusot	1.1ml injected into stomach	Daily	croens		
32	Methylcobalamin (B-12)	25mg/ml inject into buttocks	1x every 3rd day	Lyme		
33	Procrit Injection	20,000units	1x per week	severe anemia	w/blood trans.	Hospi

Stopped 5/10

Stopped 5/10

Stopped 5/10

Stopped as of 5/1/10.

Stopped as of 5/1/10.

Stopped as of 7/1/10

uped 5/1/10.

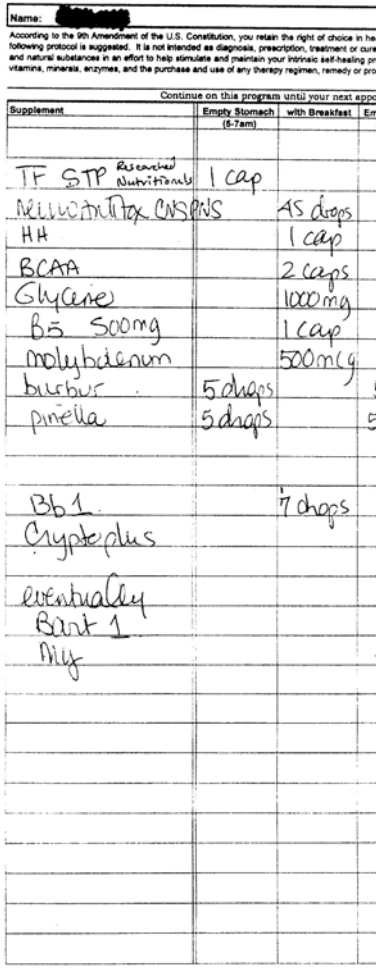
Do I still need to take?

* Advil PM- (Over the Counter) 2 tablets every night-

~~* Methadone- 10mg (1-2) tablets 3x per day.~~ (Started 5/1/10)

~~* Suboxone- (2 week titration) Pack x3~~ Started 5/1/10.

Case # 3 (LH)

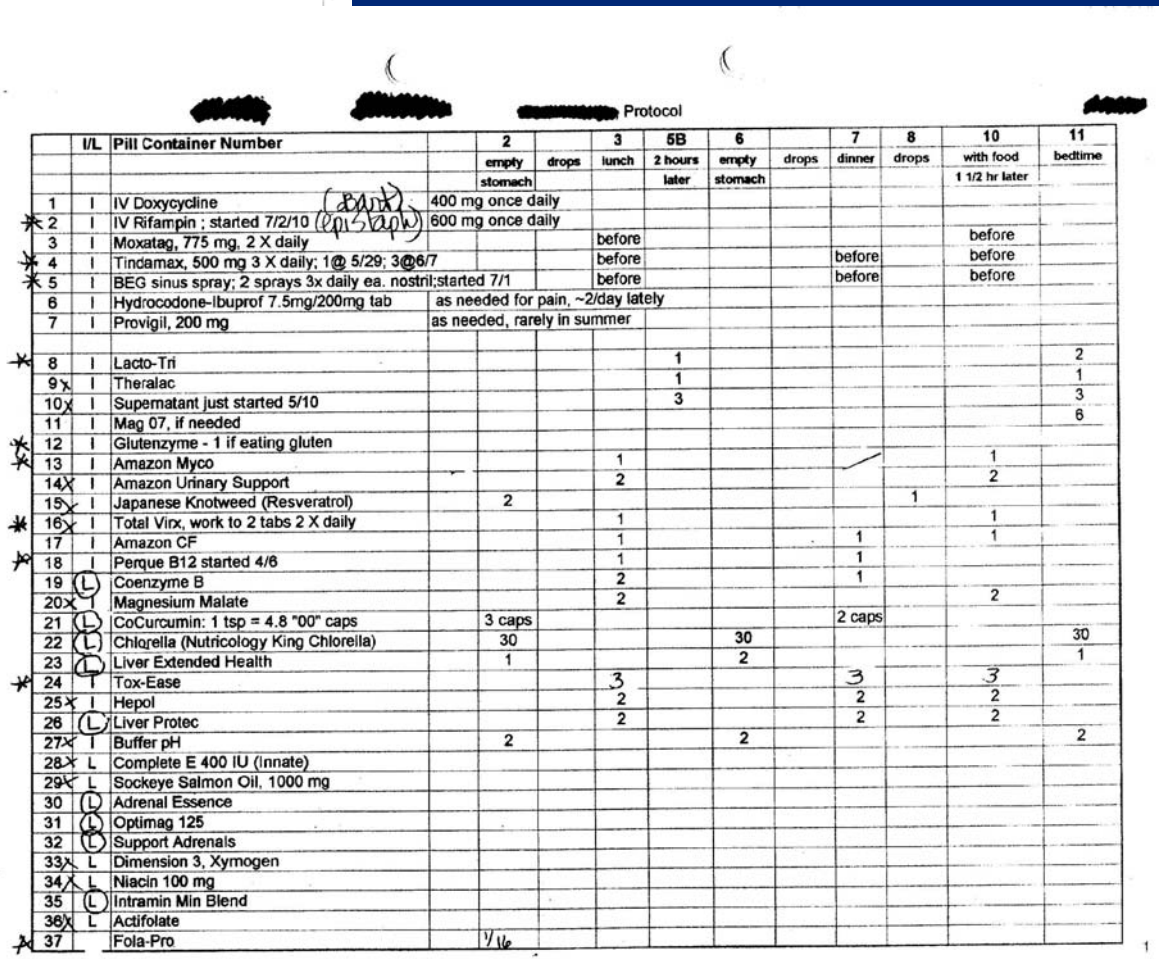


Name: [redacted]

According to the 9th Amendment of the U.S. Constitution, you retain the right of choice in he
following protocol is suggested. It is not intended as diagnosis, prescription, treatment or cure
and natural substances in an effort to help stimulate and maintain your intrinsic self-healing pr
vitamins, minerals, enzymes, and the purchase and use of any therapy regimen, remedy or pro

Continue on this program until your next appo

Supplement	Empty Stomach (6-7am)	with Breakfast	En
TF STP Researched Nutritionals	1 cap		
Neurotrx CNSPNS		AS drops	
HH		1 cap	
BCAA		2 caps	
Glycine		1000mg	
B5 500mg		1 cap	
molybdenum		500mcg	
burbur	5 drops		
pinella	5 drops		
Bb 1		7 drops	
Cryptoplus			
eventually			
Bart 1			
Nly			



[redacted] [redacted] [redacted] Protocol [redacted]

	I/L	Pill Container Number		2		3	5B	6		7	8	10	11
				empty	drops	lunch	2 hours	empty	drops	dinner	drops	with food	bedtime
				stomach			later	stomach				1 1/2 hr later	
1	I	IV Doxycycline (apart)	400 mg once daily										
* 2	I	IV Rifampin ; started 7/2/10 (apart)	600 mg once daily										
3	I	Moxatag, 775 mg, 2 X daily				before						before	
* 4	I	Tindamax, 500 mg 3 X daily; 1@ 5/29; 3@6/7				before				before		before	
* 5	I	BEG sinus spray; 2 sprays 3x daily ea. nostril;started 7/1				before				before		before	
6	I	Hydrocodone-Ibuprof 7.5mg/200mg tab	as needed for pain, ~2/day lately										
7	I	Provigil, 200 mg	as needed, rarely in summer										
* 8	I	Lacto-Tri					1						2
9 X	I	Theralac					1						1
10 X	I	Supernatant just started 5/10					3						3
11	I	Mag 07, if needed											6
* 12	I	Glutenzyme - 1 if eating gluten											
* 13	I	Amazon Myco				1						1	
14 X	I	Amazon Urinary Support				2						2	
15 X	I	Japanese Knotweed (Resveratrol)		2							1		
* 16 X	I	Total Virx, work to 2 tabs 2 X daily				1						1	
17	I	Amazon CF				1				1		1	
* 18	I	Perque B12 started 4/6				1				1			
19	(L)	Coenzyme B				2				1			
20 X	I	Magnesium Malate				2						2	
21	(L)	CoCurcumin: 1 tsp = 4.8 "00" caps		3 caps						2 caps			
22	(L)	Chlorella (Nutricology King Chlorella)		30				30					30
23	(L)	Liver Extended Health		1				2					1
* 24	I	Tox-Ease				3				3		3	
25 X	I	Hepol				2				2		2	
26	(L)	Liver Protec				2				2		2	
27 X	I	Buffer pH		2				2					2
28 X	L	Complete E 400 IU (Innate)											
29 X	L	Sockeye Salmon Oil, 1000 mg											
30	(L)	Adrenal Essence											
31	(L)	Optimag 125											
32	(L)	Support Adrenals											
33 X	L	Dimension 3, Xymogen											
34 X	L	Niacin 100 mg											
35	(L)	Intramin Min Blend											
36 X	L	Actifolate											
* 37		Fola-Pro		1/16									